Argentine Guidelines for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis in Postmenopausal Women and Men Aged 50 Years and Older

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Objective: The aim of this study was to provide an evidence-based framework to guide health care professionals treating patients under glucocorticoid (GC) therapy and develop guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis (GIO) in postmenopausal women and men aged ≥50 years.

Methods: An expert panel on bone diseases designed a series of clinically meaningful questions following the PICO (Population, Intervention, Comparator, and Outcome) structure. Using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology, we made a systematic literature review, extracted and summarized the effect estimates, and graded the quality of the evidence. The expert panel voted each PICO question and made recommendations after reaching an agreement of at least 70%.

Results: Seventeen recommendations (9 strong and 8 conditional) and 8 general principles were developed for postmenopausal women and men aged ≥50 years under GC treatment. Bone mineral density (BMD), occurrence of fragility fractures, probability of fracture at 10 years by Fracture Risk Assessment Tool, and other screening factors for low BMD are recommended for patient evaluation and stratification according to fragility fracture risk. The treatment of patients under GC therapy should include counseling on lifestyle habits and strict control of comorbidities. The goal of GIO treatment is the nonoccurrence of new fragility fractures as well as to increase or maintain BMD in certain clinical situations. This was considered for the therapeutic approach in different clinical scenarios.

Conclusions: This GIO guideline provides evidence-based guidance for health care providers treating patients.

Key Words: glucocorticoid-induced osteoporosis, guidelines, prevention, treatment

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Glucocorticoid-induced osteoporosis (GIO) is the most frequent form of secondary osteoporosis and the main cause of osteoporosis in young people. The use of long-term glucocorticoid (GC) therapy is estimated in 1% to 2% of the whole population,[1] and bone involvement has been extensively reported. The GC-induced bone loss occurs rapidly increasing the incidence of vertebral and nonvertebral fractures after 3 to 6 months of GC therapy initiation in a dose-dependent manner. The bone mineral density (BMD) loss is between 6% and 12% in the first year. Fracture risk remains increased during GC therapy and declines after its withdrawal, although it is not clear if it reverts to baseline values.[2–4]

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These guidelines and recommendations were developed and endorsed by 3 scientific societies from Argentina: AAOMM (Asociación Argentina de Osteología y Metabolismo Mineral; Argentine Association of Osteology and Mineral Metabolism), SAO (Sociedad Argentina de Osteoporosis; Argentine Osteoporosis Society), and SAR (Sociedad Argentina de Reumatología; Argentine Society of Rheumatology) and are intended to provide an evidence-based framework to guide health care professionals treating patients under glucocorticoid therapy.

AAOMM, SAO, and SAR are independent, professional, medical, and scientific societies that do not guarantee, warrant, or endorse any commercial product or service.

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Vertebral fractures are a main characteristic of GIO, although the risk of nonvertebral fractures, including hip fractures, is also increased. After 1 year of GC treatment, the incidence of new fractures can reach 17%, and some observational studies suggest that between 30% and 50% of treated patients may fracture in the longer term.[5] Fractures can occur as soon as 3 months after starting GC therapy, even with low GC doses. Van Staa et al[4] stratified the population according to doses (≤2.5, 2.5–7.5, and ≥7.5 mg/d of prednisolone or equivalent) and found a significant dose-response for all fracture sites, except for the forearm. For vertebral fracture, the relative risks (RR) were 1.55, 2.59, and 5.18, respectively; and for hip fracture, 1.77 with 2.5–7.5 mg/d and 2.27 in the highest dose group.[4]

Other risk factors for GIO and fractures are current smoking, alcoholism, low body mass index (BMI), and the current disease activity.

According to the high frequency of GC use in the population and its increased risk of fragility fractures, several guidelines for GIO were developed over time, but different diagnostic criteria and recommended treatments have been suggested.

Objectives

The aim of this study was to provide an evidence-based framework to guide health care professionals treating patients under GC therapy (≥5 mg/d prednisolone dose, or equivalent, for more than 3 months) and develop guidelines for prevention and treatment of GIO in postmenopausal women and men aged ≥50 years. The scope included therapies approved by the Argentine Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, and the US Food and Drug Administration. This guideline highlights recommendations in different clinical situations and a clinical approach for screening and monitoring patients.

Target Audience

Health care providers who are involved in the management of patients that begin or are under GC therapy. This may include rheumatologists, endocrinologists, gynecologists, traumatologists, geriatricians, internists, primary care providers or general practitioners, pharmacists, and physicians. It may also include patients under GC therapy.

METHODS

Stakeholder Involvement

This guideline has been made and endorsed by 3 scientific societies from Argentina: AAOMM (Asociación Argentina de Osteología y Metabolismo Mineral; Argentine Association of Osteology and Mineral Metabolism), SAO (Sociedad Argentina de Osteoporosis; Argentine Osteoporosis Society), and SAR (Sociedad Argentina de Reumatología; Argentine Society of Rheumatology) (Supplemental Digital Content 1, http://links.lww.com/RHU/A572; Supplemental Digital Content 2, http://links.lww.com/RHU/A573). It was developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[6] methodology. The expert panel defined the scope of this guideline, generated the Population, Intervention, Comparator, and Outcome (PICO) questions (Supplemental Digital Content 3, http://links.lww.com/RHU/A574) and conducted the voting process.

Literature Search

A systematic literature search for published randomized controlled trials, nonrandomized trials, cohort studies, and post hoc analysis was performed in MEDLINE/PubMed, the Cochrane Library, and LILACS from the beginning of each database up to October 2020, and gray literature of the last 4 years was also searched for (Supplemental Digital Content 4, http://links.lww.com/RHU/A575). Only articles in English, Portuguese, or Spanish were considered.

Study Selection

The literature search was performed using Rayyan software (https://rayyan-prod.qcri.org/), and duplicate screening of each title/abstract was performed by 2 independent reviewers. Eligible articles underwent full-text screening by 2 independent reviewers. In both steps, a third reviewer was responsible for solving conflicts, if needed. Selected manuscripts were matched to PICO questions (Supplemental Digital Content 3, http://links.lww.com/RHU/A574).

Data Extraction, Analysis, and Quality Assessment

Pooling of the data for statistical analysis was done using Review Manager (RevMan, software V.5.4.1; Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration). For dichotomous variables, the number of events in both groups was registered as the total number of participants. With these data, the absolute risk and the RR were calculated. In the case of continuous variables, the mean difference of each group was registered as well as the p value.[7] The critical/important outcomes (fractures and adverse events) selected for this guideline were binary, and they were analyzed using the Mantel-Haenszel method in a fixed-effects model and reported as RR (95% confidence intervals). In clinical scenarios not addressed by randomized controlled trial data, we used data from observational cohort studies to estimate relative effects. For BMD, the percentage (%) of change was evaluated as a continuous variable and was analyzed using inverse variance as statistical method in a fixed-effects model. When meta-analysis was feasible, RR was calculated using a fixed-effects model to derive pooled estimates of effect size. When interstudy variability was suspected or significant heterogeneity was detected, a random-effects model was chosen. A p value <0.05 was considered significant. Statistical heterogeneity was planned to be assessed using the I^2 statistic, with the degree of heterogeneity graded as follows: <25% no heterogeneity, 25%–49% low heterogeneity, 50%–74% moderate heterogeneity, and ≥74% high heterogeneity.[8]

The quality assessment and publication bias of randomized controlled trials were judged using the Cochrane risk of bias tool (http://handbook.cochrane.org/). For nonrandomized controlled trials, the assessment was performed using the Newcastle-Ottawa Scale.[9]

Evidence Report Formulation

To formulate the GRADE profile (Supplemental Digital Content 6, http://links.lww.com/RHU/A577) for each PICO question, we used GRADEpro Guideline Development Tool Software (McMaster University and Evidence Prime, 2021). The quality of evidence for each outcome was evaluated by 2 independent reviewers using GRADE quality assessment criteria, and potential discordances were resolved through discussion with the participation of a third reviewer.[10] The use of BMD as a surrogate outcome requires rating down the quality of evidence by 1 level for indirectness.

The GRADE methodology differentiates 4 levels of evidence quality (ie, high, moderate, low, or very low) based on the degree of confidence that the measure of the effect reached after the analysis of the grouped studies is close to the true effect.[11] If a recommendation was made based on consensus of expert opinions in the

absence of evidence, this recommendation was graded as very low quality.

Moving From Evidence to Recommendations

GRADE methodology stipulates that the experts make recommendations based on the balance of quality of the evidence, benefits, and eventual adverse effects, and patient's preferences.

Consensus Building

The voting panel decided on the direction and strength of the recommendation for each PICO question. A recommendation could be either for or against the proposed intervention, and be qualified either as being strong or conditional. In some cases, the voting panel combined PICO questions into 1 recommendation for clarity. All recommendations required achieving a 70% level of agreement.[12]

Moving From Recommendations to Practice

Although these recommendations are designed to help health professionals, they must take into consideration the underlying diseases, other comorbidities, presence of fragility fracture, and other clinical features.

Rigor of Development

This guideline has been developed under the GRADE methodology and abides by the AGREE Reporting Checklist to ensure the transparency of this clinical practice guidelines.[13]

Areas the Guideline Does Not Cover

Patients with organ transplants, chronic kidney disease (stage 4–5), under inhaled GC therapy, and under high GC doses or bolus were not included in this guideline. Also, pediatrics, premenopausal women, and men aged <50 years were not included.

Disclosures and Management of Conflicts of Interest

Individuals whose primary occupation was a position in a company that manufactures or sells therapeutics or diagnostic devices were not considered to participate.

RESULTS

A summary of the categories considered by the expert panel is shown in Table 1. The recommendations are based on a total of 54 PICO questions. The literature review initially identified 1214 manuscripts, but finally, 40 articles were considered for the evidence report (see flowchart in Supplemental Digital Content 5, http://links.lww.com/RHU/A576). The literature review identified evidence for 33.3% (n = 18) of the PICO questions, for which 17 recommendations (9 strong and 8 conditional) were developed and are detailed in Table 2.

Recommendations for Postmenopausal Women or Men Aged ≥50 Years Under GC therapy (Doses ≥5 mg/d of Prednisolone, or Equivalent, for More than 3 Months)

Calcium, Vitamin D, and Physical Activity

Recommendation 1: Calcium and vitamin D are strongly recommended over placebo in postmenopausal women or men aged ≥50 years under GC therapy in both prevention and treatment.

The recommendation was considered strong despite the moderate/low level of evidence.[14–16] For patients under GC therapy, clinical experience and indirect evidence support the benefits of adding calcium and vitamin D. Although critically important adverse events were not considered in the analyzed studies, the treating physician must take them into consideration in the management of these patients.

Chronic calcium deficiency due to low intake or impaired intestinal absorption is one of the main causes of reduced bone mass. Therefore, adequate calcium intake is essential for healthy bones. Patients may increase their daily intake by consuming calcium-rich foods and, if necessary, calcium supplements.[17,18] The recommended daily calcium intake in this population is 1200 mg/d. From the different available forms of calcium salts, calcium citrate and calcium carbonate complexes are the most frequently used. These calcium supplements may be suggested based on certain clinical characteristics of the patients (Supplemental Digital Content 7, http://links.lww.com/RHU/A578).[19] Patients with a history of nephrolithiasis or hypercalciuria should be evaluated for the etiology of both clinical situations before making a

TABLE 1. Description of Each Category

Category	Description
Low-dose GC	<5 mg/d of prednisolone (or equivalent)
Medium-dose GC	5 to 7.5 mg/d of prednisolone (or equivalent)
High-dose GC	≥7.5 mg/d of prednisolone (or equivalent)
Short-term GC	<3 mo of GC therapy
Long-term GC	≥3 mo of GC therapy
Normal BMD	T-score > −1
Low bone mass (osteopenia)	T-score between −1 and −2.4
Osteoporosis	T-score ≤ −2.5
Threshold for treatment in patients under GC therapy	T-score ≤ −1.7
Significant decrease in BMD	≥5% in at least 2 serial BMD measurements at the lumbar spine or ≥4% at the proximal femur
Moderate risk of fracture	Patients without fractures, BMD T-score ≤ −1.7, and a probability of fracture at 10 y by adjusting FRAX <20% for MOF and <3% for hip fracture
High risk of fracture	Fragility fractures in the last 24 mo or probability of fracture at 10 y by adjusting FRAX >20% for MOF and >3% for hip fracture
Very high risk of fracture	Fragility fractures in the last 12 mo or multiple fragility fractures or fractures during GIO treatment or probability of fracture at 10 y of MOF by adjusting FRAX >30% and >4.5% for hip fracture

TABLE 2. Recommendations for Patients Under GC Therapy With Doses ≥5 mg/d of Prednisolone or Equivalent in Postmenopausal Women or Men Aged ≥50 Years

Recommendations	Evidence
1. Calcium and vitamin D are strongly recommended over placebo in postmenopausal women or men aged ≥50 y under GC therapy in both prevention and treatment.	Moderate to low
2. Eldecalcitol is conditionally recommended over alfacalcidol in postmenopausal women and men aged ≥50 y under GC therapy.	Low
3. Exercises/physical activity is strongly recommended in postmenopausal women or men aged ≥50 y under GC therapy in both prevention and treatment.	Very low
4. Alendronate is strongly recommended over placebo in postmenopausal women or men aged ≥50 y who are under GC therapy and meet the DXA threshold for receiving treatment or present fragility fractures or are at high/moderate risk of fractures.	High to very low
5. Alendronate is strongly recommended over alfacalcidol in postmenopausal women or men aged ≥50 y who are under GC therapy and meet the DXA threshold for receiving treatment or present fragility fractures or are at high/moderate risk of fractures.	High to low
6. Alendronate is conditionally recommended against over risedronate in postmenopausal women or men ≥50 y who are under GC therapy and meet the DXA threshold for receiving treatment or present fragility fractures or are at high/moderate risk of fractures.	Low to very low
7. Risedronate is strongly recommended over placebo in postmenopausal women or men aged ≥50 y who are under GC therapy and meet the DXA threshold for receiving treatment or present fragility fractures or are at high/moderate risk of fractures.	Moderate to very low
8. Oral ibandronate is strongly recommended over placebo in postmenopausal women or men aged ≥50 y who are under GC therapy and meet the DXA threshold for receiving treatment or present fragility fractures or are at high/moderate risk of fractures.	Moderate to very low
9. Intravenous ibandronate is conditionally recommended over alfacalcidol in postmenopausal women or men aged ≥50 y who are under GC therapy and meet the DXA threshold for receiving treatment or present fragility fractures or are at high/moderate risk of fractures.	Low to very low
10. Pamidronate is strongly recommended over calcium in postmenopausal women or men aged ≥50 y who are under GC therapy and meet the DXA threshold for receiving treatment or present fragility fractures or are at high/moderate risk of fractures.	Low to very low
11. Zoledronate is conditionally recommended over risedronate in postmenopausal women or men ≥50 y who are under GC therapy and present fragility fractures or are at very high/high risk of fractures.	Moderate to low
12. Denosumab is conditionally recommended over alendronate in postmenopausal women or men ≥50 y who are under GC therapy and present fragility fractures or are at very high/high risk of fractures.	Very low
13. Denosumab is conditionally recommended over risedronate in postmenopausal women or men ≥50 y who are under GC therapy and present fragility fractures or are at very high/high risk of fractures.	High to low
14. Teriparatide is strongly recommended over alendronate in postmenopausal women or men ≥50 y who are under GC therapy and present fragility fractures or are at very high/high risk of fractures.	High to low
15. Teriparatide is strongly recommended over estrogen in postmenopausal women who are under GC therapy and present fragility fractures or are at very high/high risk of fractures.	Low
16. Raloxifene is conditionally recommended over calcium supplements in postmenopausal women under GC therapy for those who meet the DXA threshold for receiving treatment.	Low to very low
17. Switching bisphosphonates to denosumab is conditionally recommended for postmenopausal women or men aged ≥50 y under GC therapy.	Low to very low

decision on calcium supplementation. Since high sodium intake may increase urine calcium, reduction or restriction of sodium intake should be advised according to each clinical case.

Vitamin D is a hormone with an essential role in calcium homeostasis and bone metabolism, muscle function, and in innate and adaptive immune function. Vitamin D doses should be indicated after being titrated based on vitamin D levels, and serum and urinary calcium values. In individuals with hypercalcemia or hypercalciuria, daily supplementation of vitamin D is recommended instead of bolus doses. Therefore, decisions about the appropriate formulation and vitamin D level will be made according to each clinical case.

Recommendation 2: Eldecalcitol is conditionally recommended over alfacalcidol in postmenopausal women and men aged ≥50 years under GC therapy.

Only one study was included for this PICO.[20] e-GLORIA (eldecalcitol for GC-induced osteoporosis vs alfacalcidol) was a multicenter, randomized, open-label, parallel-group clinical study. There were no significant differences between groups, considering the outcome fractures (at 24 months) and adverse events.

The recommendation was based on the low quality of the evidence and only on a surrogate outcome as BMD, without considering the experts' experience because eldecalcitol and alfacalcidol are not available in Argentina at the time of writing this guideline. However, the difference in BMD is below the percentage of change considered by the expert panel, and therefore there would be no clinical differences, and both eldecalcitol and alfacalcidol could be considered.

Recommendation 3: Exercise/physical activity is strongly recommended in postmenopausal women or men aged ≥50 years under GC therapy in both prevention and treatment.

The recommendation is based on the experience of experts, not on the quality of the evidence. The outcomes of fractures were not evaluated. Although there is insufficient data,[21] the benefit of physical activity, according to age, on skeletal muscle tissue is significant.

Bisphosphonates

Recommendation 4: Alendronate is strongly recommended over placebo in postmenopausal women or men aged ≥50 years who are under GC therapy and meet the dual-energy x-ray absorptiometry (DXA) threshold for receiving treatment or present fragility fractures or are at high/moderate risk of fractures.

Eight studies evaluated the efficacy and security of alendronate.[22–29] Alendronate significantly reduced vertebral fractures compared with placebo. The quantitative analysis indicated that alendronate prevented hip fractures[20,21] and also reduced major osteoporotic fractures compared with placebo.[20,22,24] Alendronate also increased femoral neck, total hip, and lumbar spine BMD in both women and men receiving GC therapy.[19,26]

Recommendation 5: Alendronate is strongly recommended over alfacalcidol in postmenopausal women or men aged ≥50 years who are under GC therapy and meet the DXA threshold for receiving treatment or present fragility fractures or are at high/moderate risk of fractures.

Alendronate versus alfacalcidol was evaluated in 3 clinical trials.[30–32] Alendronate showed effectiveness in the prevention of GC-induced bone loss compared with alfacalcidol in femoral neck, total hip, and lumbar spine BMD. In addition, de Nijs et al[30] showed that alendronate significantly reduced the risk of vertebral fractures versus alfacalcidol at 18 months. As adverse effects, hypocalcemia was higher in patients under alendronate treatment, whereas hypercalcemia was higher in patients using alfacalcidol. The recommendation was based on the quality of the evidence and the long-term experience with alendronate.

Recommendation 6: Alendronate is conditionally recommended against over risedronate in postmenopausal women or men aged ≥50 years who are under GC therapy and meet the DXA threshold for receiving treatment or present fragility fractures or are at high/moderate risk of fractures.

Osteoporotic fractures in patients treated with alendronate versus risedronate were evaluated in 3 observational studies, which were not designed to compare drugs.[20,33,34] Despite this consideration, both drugs decreased clinical vertebral and nonvertebral fractures, but when comparing them in the quantitative analysis, there were no significant differences.[30,31] Considering that the evidence to report that alendronate is superior to risedronate is weak, based on the evidence and the experience of experts, both are recommended in the same line of treatment.

Recommendation 7: Risedronate is strongly recommended over placebo in postmenopausal women or men aged ≥50 years who are under GC therapy and meet the DXA threshold for receiving treatment or present fragility fractures or are at high/moderate risk of fractures.

Risedronate versus placebo was studied in patients under chronic GC therapy at different doses (GC <7.5 and ≥7.5 mg/d of prednisolone or equivalent).[22,35–40] Risedronate reduced hip and vertebral fracture compared with placebo, and significantly increased femoral neck and lumbar spine BMD at different times.[20,32,33] No differences between risedronate and placebo were found in esophagitis, esophageal, and gastric ulcers adverse events. This recommendation was approved unanimously by the voting panel independently of GC doses.

Recommendation 8: Oral ibandronate is strongly recommended over placebo in postmenopausal women or men aged ≥50 years who are under GC therapy and meet the DXA threshold for receiving treatment or present fragility fractures or are at high/moderate risk of fractures.

Ibandronate demonstrated security and significantly increased femoral neck and lumbar spine BMD versus placebo.[41,42] There is an evident lack of studies in the population under GC for evaluating its antifracture efficacy. No differences between risedronate and placebo were found in gastric ulcers and osteonecrosis of the jaw adverse events. Therefore, the voting panel strongly recommended ibandronate over placebo based on experience and safety in GC-treated patients.

Recommendation 9: Intravenous ibandronate is conditionally recommended over alfacalcidol in postmenopausal women or men aged ≥50 years who are under GC therapy and meet the DXA threshold for receiving treatment or present fragility fractures or are at high/moderate risk of fractures.

Only one study comparing intravenous ibandronate versus alfacalcidol was conducted.[43] Ibandronate injections showed significantly greater increases in femoral neck and lumbar spine BMD versus daily oral alfacalcidol. The recommendation is conditional because intravenous ibandronate would be an option in patients with previous fragility fractures, osteoporosis diagnosis, very high or high risk of fractures, and particularly in those with gastric intolerance to oral bisphosphonates. In addition, it has a higher cost than oral bisphosphonates and requires access to a center for the administration of the intravenous infusion.

Recommendation 10: Pamidronate is strongly recommended over calcium in postmenopausal women or men aged ≥50 years who are under GC therapy and meet the DXA threshold for receiving treatment or present fragility fractures or are at high/moderate risk of fractures.

Despite the low quality of evidence,[44,45] and based on BMD and the experts' experience, the voting panel recommended its indication if other active drug on the bone is not available since pamidronate is a well-known and low-cost drug. In addition, no differences in adverse events such as myalgias and uveitis were found. Furthermore, the recommendation for calcium is to be used as adjunct therapy.

Recommendation 11: Zoledronate is conditionally recommended over risedronate in postmenopausal women or men aged ≥50 years who are under GC therapy and present fragility fractures or are at very high/high risk of fractures.

High-quality evidence to recommend zoledronate over risedronate is not available in GC-treated patients. Nevertheless, significant differences were found in BMD in the zoledronate group. Zoledronate was neither inferior nor superior to risedronate when considering the increase in lumbar spine BMD in both the treatment and the prevention groups.[46] In addition, significant differences were observed in both treatment and prevention groups in total hip and femoral neck. Until further evidence is available, the voting panel recommends zoledronate over risedronate in patients under GC therapy with previous fragility fractures or very high risk of fractures, or contraindication or intolerance to oral bisphosphonates.

Denosumab

Recommendation 12: Denosumab is conditionally recommended over alendronate in postmenopausal women or men aged ≥50 years who are under GC therapy and present fragility fractures or are at very high/high risk of fractures.

This recommendation is based on that both drugs have been demonstrated to be safe and effective in patients with osteoporosis.[47] Nevertheless, in patients under GC therapy, there is a very low quality of evidence comparing denosumab versus alendronate.[48] Therefore, the voting panel based on experience recommends denosumab in patients under GC therapy with previous fragility fractures or very high or high risk of fractures.

Recommendation 13: Denosumab is conditionally recommended over risedronate in postmenopausal women or men aged ≥50 years who are under GC therapy and present fragility fractures or are at very high/high risk of fractures.

Only one noninferiority study evaluated denosumab versus risedronate in subjects in continuing and GC-initiating subpopulations.[49] There was no difference in vertebral and nonvertebral fractures at evaluated times (12 and 24 months). Nevertheless, a slight trend in favor of denosumab was observed in the analysis of vertebral fractures. Denosumab improved total hip and lumbar spine BMD in initiating, and GC-continuing patients, being superior to risedronate.[50] The voting panel recommends denosumab, particularly in patients under GC therapy with previous fragility fractures or very high or high risk of fractures.

Teriparatide

Recommendation 14: Teriparatide is strongly recommended over alendronate in postmenopausal women or men aged ≥50 years under GC therapy and present fragility fractures or are at very high/high risk of fractures.

Daily teriparatide versus alendronate was examined in GC-treated patients in 3 reports.[51–53] Teriparatide significantly decreased the risk of vertebral fractures and increased total hip and lumbar spine BMD compared with alendronate at 18 and 36 months. However, hypercalcemia was more frequent in the teriparatide group. The voting panel strongly recommends teriparatide over alendronate in patients under GC therapy with a significant decrease in BMD, previous fragility fractures, or very high or high risk of fractures. This recommendation was based on experience, quality of evidence, and mechanism of action.

Recommendation 15: Teriparatide is strongly recommended over estrogen in postmenopausal women who are under GC therapy and present fragility fractures or are at very high/high risk of fractures.

Despite the low quality of evidence,[54] this voting panel strongly recommends teriparatide over estrogen in patients under GC therapy with a significant decrease in BMD, or previous fragility fractures, or very high or high risk of fractures. This recommendation was based on BMD and voting panel experience.

Raloxifene

Recommendation 16: Raloxifene is conditionally recommended over calcium supplements in postmenopausal women under GC therapy for those who meet the DXA threshold for receiving treatment.

Only 2 trials evaluated raloxifene in patients under GC therapy[55,56] showing better BMD in the raloxifene group. If another active drug on the bone is not available, raloxifene could be indicated in patients under GC therapy. Nevertheless, the position of the expert panel concerning raloxifene is conditional due to its possible adverse effects as thromboembolic events and its higher risk in patients with connective tissue diseases. The undesirable effects would outweigh its desirable effects on bone in the subgroup of patients with collagen disorders.

Switching Bisphosphonates to Denosumab

Recommendation 17: Switching bisphosphonates to denosumab is conditionally recommended for postmenopausal women or men aged ≥50 years under GC therapy.

Only one trial evaluated adult patients receiving long-term prednisolone and oral bisphosphonates (≥2 years). Patients were randomized to continue with oral bisphosphonates or switch to 60 mg of subcutaneous denosumab every 6 months.[57] The recommendation was based on the experience of experts, and not on the quality of the evidence because data are insufficient. Nevertheless, the switch from bisphosphonates to denosumab could be done in patients who had already experienced new fragility fractures, new vertebral fractures, persisted on very high or high risk fractures, or in those in whom a significant decrease in BMD is observed despite bisphosphonates.

In addition, 8 general principles were written by mutual agreement of all panel members. These general principles demonstrate points of importance in the management of these patients (Table 3). As these general principles were based on consensus of expert opinions in the absence of evidence, the evidence for these recommendations was graded as very low quality.

GENERAL CONSIDERATIONS OF TREATMENT APPROACH

General considerations were made according to the expertise of the panel, and the known evidence in the management and follow-up of patients with osteoporosis.[58] All considerations made on the management and therapeutic follow-up of patients with GIO were subject to discussion and agreed on unanimously by the panel.

Evaluation of Patients Under GC Therapy

The following recommendations are for postmenopausal women or men aged ≥50 years using ≥5 mg/d of prednisolone or equivalent.

Screening for risk of low bone mass should be performed immediately upon GC therapy initiation or as soon as possible:

TABLE 3. Guiding Principles

1 Treatment of patients under GC therapy should include counselling on lifestyle habits and strict control of comorbidities. Smoking, intake of alcoholic beverages, obesity, and a sedentary lifestyle should be strongly discouraged. The appropriate management of comorbidities, particularly autoimmune diseases, diabetes mellitus, sarcopenia, endocrinologic disease, and any disease or drugs (except for GC) that could affect bone metabolism, are part of the care of patients under GC therapy.

2 Treatment with GC should be limited to the lowest effective dose for the shortest possible duration. The toxicity associated with GC was judged to outweigh the potential benefits.

3 The gold standard method to study BMD is bone densitometry by DXA, which should be done at baseline and annually while patients persist under GC therapy or persist under GIO treatment.

4 Bone turnover markers and the evaluation of subclinical vertebral fractures are as important as BMD evaluation. In addition, the evaluation of the risk of fracture should be performed.

5 GIO treatment should be based on decisions shared by the patient and physician after understanding the different available therapeutic options, cost, route of administration, and possible adverse events.

6 The goal of GIO treatment is the nonoccurrence of new fragility fractures as well as to increase BMD.

7 Consider calcium supplements if daily requirements are not reached with diet intake.

8 Baseline vitamin D measurement is recommended and vitamin D supplements until optimal values are achieved.

- A complete medical history with an emphasis on a history of osteoporotic personal and family fractures, other secondary causes of low bone mass (premature menopause, celiac disease, malabsorption, chronic malnutrition, hyperthyroidism, hyperparathyroidism, hypogonadism, type 1 diabetes mellitus, chronic kidney disease, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic liver disease, among others), and drugs with negative effects on bone mass, except GC (ie, cyclosporine, loop diuretics, anticonvulsants, heparin, etc).
- Evaluation of muscle assessment and possible causes that increase the risk of falls.
- Consider other risk factors useful in the assessment of fracture risk, such as age ≥65, female gender, ethnicity (White and Asian populations), low body weight, or low BMI (<20 kg/m^2), alcohol intake of 3 or more units a day, current smoking, early menopause, estrogen deficiency and amenorrhea, previous fragility fracture, family history of fragility fractures, low dietary calcium intake, vitamin D deficiency, height loss, insufficient exercise, frequent falls, other diseases that can affect bone metabolism, and other medications, except GC, that could negatively affect bone metabolism.
- Baseline physical examination includes height and weight, as well as somatic characteristics of the patient (kyphosis, use of walking assistance devices, etc).

Recommended Measurements in Patients Under GC Therapy

General Clinical Biochemistry

This expert panel suggests considering a general and bone metabolism biochemistry for baseline screening to look for other contributors to/risk factors for osteoporosis/fracture at the time of GC therapy initiation and every 6 months.

- Basal general and bone metabolism biochemistry: blood count, uremia, creatinine, hepatogram, albumin; serum: calcium, phosphate, magnesium, parathyroid hormone, 25(OH) vitamin D levels; 24-hour urine: calcium, phosphate, creatinine.
- Bone markers: bone formation: alkaline phosphatase, bone-specific alkaline phosphatase, osteocalcin, and *N*-terminal propeptide of type I procollagen; bone resorption: *N*-terminal telopeptide of type I collagen, C-terminal telopeptide of type I collagen, urinary deoxypyridinoline. It is suggested to measure at least 1 bone formation marker and 1 bone resorption marker and follow-up with the same markers in those patients at baseline and every 6 months under GIO therapy.
- 25(OH) vitamin D levels (25OHD). This expert panel suggested measuring serum 25OHD levels in patients under GC therapy and classifying them according to the following categories: severe deficiency, <10 ng/mL; deficiency, 10–19 ng/mL; insufficiency, 20–29 ng/mL; and optimal levels, ≥30 ng/mL.[59]
- If necessary, according to each clinical case: electrophoretic proteinogram, thyroid hormone or thyroid-stimulating hormone, cortisol, FSH, estradiol, testosterone, and celiac antibodies.[14]

Bone Mineral Density by DXA

Bone mineral density measurement is suggested in those patients with conditions associated with low bone mass or bone loss according to ISCD official position. Bone mineral density of patients under GC therapy should be evaluated as soon as possible. The skeletal sites to assess are the postero-anterior lumbar spine, femoral neck, and total hip BMD. Forearm BMD should be considered when hip and/or lumbar spine cannot be measured or interpreted, in subjects with hyperparathyroidism, or in patients over the weight limit for DXA measurement technique limit.[58]

Regarding indications of bone densitometry by DXA in patients under GC therapy, BMD should be assessed:

- In all cases under GC treatment, a basal BMD by DXA is recommended.
- In individuals starting long-term (≥3 months) GC therapy.
- In individuals starting short-term (<3 months) GC therapy with high GC doses.
- In individuals under GIO treatment.
- Although individuals are under GC therapy, an annual BMD by DXA should be performed.
- In individuals in whom treatment should be switched or discontinued.

After the analysis of previous studies[60–62] considering a BMD threshold of fractures in GIO, we considered a T-score −1.7 for treatment in postmenopausal women and men ≥50 years old under GC therapy.

Standard Lateral Spine Radiography or Vertebral Fracture Assessment

The presence of vertebral fractures must be investigated through dorsal and lumbar lateral spine radiography or vertebral fracture assessment in all patients who are initiating or are under GC therapy, also, in patients with unexplained height loss, or who self-reported prior vertebral fractures, but which are undocumented. Vertebral fracture assessment by DXA is the best initial or basal assessment for detecting vertebral fractures.[58] Fracture diagnosis should be based on visual evaluation and include assessment of grade/severity according to Genant et al.[63]

Vertebral fracture assessment or lateral spine radiography should be repeated in patients with persistent high risk of fracture.

Fracture Risk Assessment Tool

Fracture Risk Assessment Tool (FRAX) is a tool to estimate the 10-year probability of hip and major osteoporotic fractures (clinical spine, forearm, hip, or humerus) with or without the femoral neck BMD. Fracture Risk Assessment Tool also integrates clinical risk factors (previous fragility fracture, parental history of hip fracture, GC therapy, smoking, alcohol intake, low BMI, secondary osteoporosis, and rheumatoid arthritis), which, in addition to age and sex, contribute to fracture risk independently of BMD.[64] Country-specific FRAX should be used to assess fracture probability in individuals under GC therapy.

It is essential to note that FRAX considers the use of CG as a dichotomous variable, not considering the dose or duration of treatment assuming a dose between 2.5 and 7.5 mg/d of prednisolone or equivalent.[65] In patients using a prednisone dose >7.5 mg/d, the risk of major osteoporotic fracture should be increased by 1.15, and the risk of hip fracture by 1.2. However, this adjustment may not adequately estimate the risk associated with high-dose GC use.[66] Moreover, the FRAX tool uses femoral neck BMD, but the main bone impact of GC is on trabecular bone, reflecting in lumbar spine BMD.

Based on the categories used in the management of osteoporosis in postmenopausal women,[17,18] we considered ≥20% for major osteoporotic fractures and ≥3% for hip fracture as thresholds in GIO.

Trabecular Bone Score

The Trabecular Bone Score (TBS) is a parameter determined from gray-level analysis of lumbar spine DXA images based on

the mean thickness and volume fraction of trabecular bone microarchitecture.[67] Trabecular Bone Score is a better discriminator of vertebral fractures induced by GC compared with BMD from DXA.[68] Florez et al[69] found that 52% of patients receiving GC therapy for autoimmune diseases had degraded microarchitecture. In addition, degraded microarchitecture was significantly more common than osteoporosis by DXA in patients with vertebral fracture and with any fragility fracture.[69] Trabecular Bone Score enhances the performance of the FRAX tool by adjusted for TBS, and the calculated 10-year probability of fracture have been shown to be more accurate when computed including TBS.[55,70] However, it may not be available everywhere.

Fracture Risk Stratification

Several factors contribute significantly to fracture risk in addition to BMD by DXA: age, sex, low BMI, personal previous fragility fracture, parental history of hip fracture, smoking or alcoholism, GC therapy, and other causes of secondary osteoporosis.[71] The risk stratification categories considered were based on the categories used in the management of osteoporosis in postmenopausal women.[14,15] The "low risk" category was not considered for patients under GC therapy.

Therapeutic Approach in Postmenopausal Women and Men Aged ≥50 Years Under GC Therapy

If the patient does not have fragility fractures, the BMD T-score is higher than −1.7, and the probability of fracture at 10 years by adjusting FRAX is <20% for major osteoporotic fractures and <3% for hip fracture, the expert panel recommends modifying lifestyle, physical exercise, adequate calcium intake, and vitamin D supplementation. Furthermore, a clinical follow-up is recommended every 6 months, and annual bone densitometry by DXA is suggested (Fig. 1).

For treatment, we considered a BMD T-score of −1.7 or lower, fragility fractures independently of BMD, or a probability of fracture at 10 years by adjusting FRAX >20% for major osteoporotic fractures and >3% for hip fracture (Fig. 1).

The treatment recommendations were made according to fracture risk stratification (Fig. 2).

- In patients with moderate risk of fracture, the expert panel recommends oral bisphosphonates as the first option of treatment, except when contraindications or special consideration apply in each clinical case. Raloxifene or hormone replacement therapy

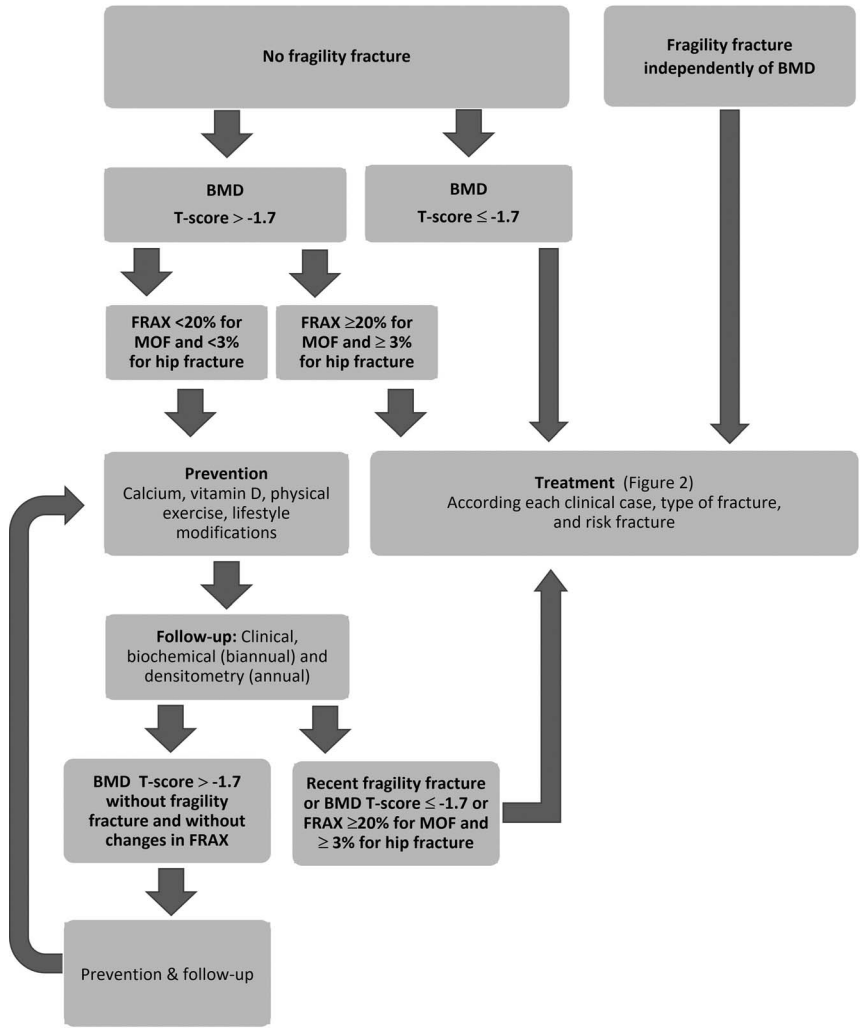

FIGURE 1. Algorithm for the management of prevention and treatment of glucocorticoid-induced osteoporosis (GIO) in postmenopausal women and men aged ≥50 years. FRAX adjustment: in patients using prednisone dose >7.5 mg/d, the risk of major osteoporotic fracture should be increased by 1.15, and the risk of hip fracture by 1.2. Color online-figure is available at http://www.jclinrheum.com.

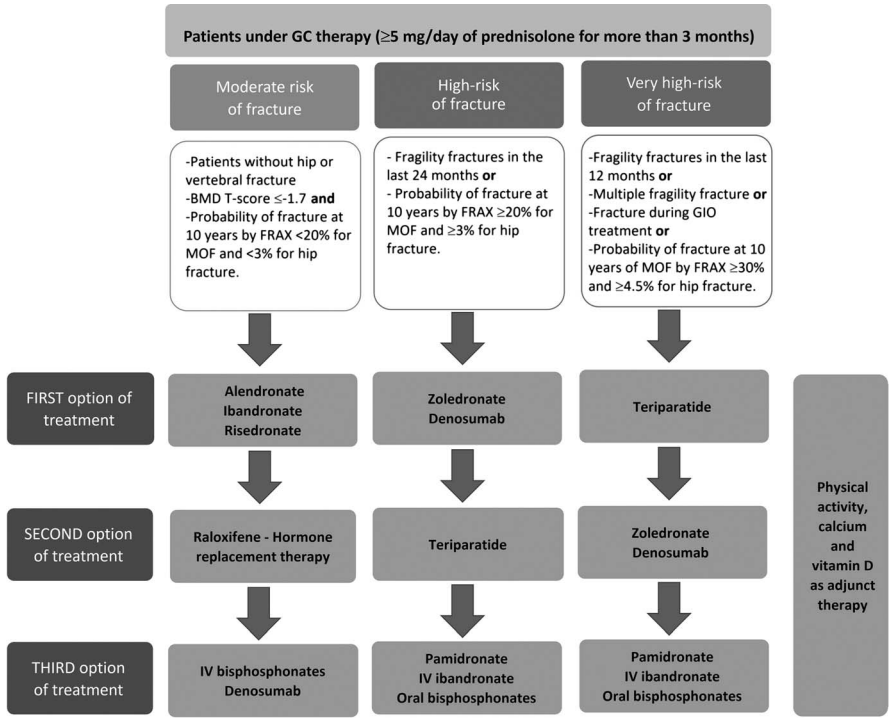

FIGURE 2. Fracture risk stratification and recommendation of treatment in postmenopausal women and men aged ≥50 years under GC therapy (≥5 mg/d of prednisolone or equivalent for more than 3 months). The risk stratification categories were based on the categories used in the management of osteoporosis in postmenopausal women.[17,18] The "low risk" category was not considered for patients under GC therapy. FRAX adjustment: in patients using prednisone dose >7.5 mg/d, the risk of major osteoporotic fracture should be increased by 1.15, and the risk of hip fracture by 1.2. Although romosozumab has been recently approved for severe osteoporosis in postmenopausal women, there is not enough evidence at the moment of the systematic review to be included. Color online-figure is available at http://www.jclinrheum.com

is considered as the second option of treatment due to its possible adverse effects.

- In patients with high risk of fracture, experts recommend zoledronate or denosumab as the first option of treatment. If this is not possible, teriparatide is suggested as the second line of treatment, and IV or oral bisphosphonates as the third option.
- In patients with very high risk of fracture, experts recommend teriparatide as the first-line therapeutic option. If teriparatide is not an option, denosumab or zoledronate is proposed as the second option, and other IV or oral bisphosphonates are suggested as the third option.

Notes:

- Calcium and vitamin D supplementation should be considered as adjuvant therapy in all fracture risk categories.
- Reconsider treatment in case of decline in BMD: ≥5% in at least 2 serial BMD measurements at the lumbar spine or ≥4% at the proximal femur.
- It is important to consider the full period of administration of each drug and evaluate if discontinuation or switch to another drug is necessary.
- Bisphosphonates: After 5 years, a drug holiday should be considered. If bisphosphonates (oral or intravenous) are discontinued, they can be stopped without the need of switch to another drug.
- Denosumab: Evidence to 10 years in postmenopausal women (not in GIO). If denosumab is discontinued, a switch to another antiresorptive drug should be considered.
- Teriparatide: Up to 2 years. If teriparatide is discontinued, a switch to an antiresorptive drug should be considered.

The different drugs, their doses, and warnings are described in Supplemental Digital Content 7, http://links.lww.com/RHU/A578.

Follow-up of Postmenopausal Women and Men Aged ≥50 Years Under GC Therapy

In patients under prevention therapy or under treatment for GIO, this panel recommends the following:

- Evaluating the correct calcium and vitamin D intake in each visit according to the supplementation prescribed.
- Evaluating physical exercise adherence.
- In patients under GIO treatment, evaluating adherence to the prescribed therapy.
- In patients under GC therapy for more than 3 months, BMD measurement by DXA should be performed before or at the beginning of treatment and then annually.
- Evaluating annually the height of patients to detect height loss.
- Radiography or vertebral fracture assessment should be performed before or at the beginning of GC therapy and annually if GC treatment persists.
- Monitoring bone markers of bone formation and bone resorption according to treatment.

DISCUSSION

This guideline was developed to provide an evidence-based framework to guide health care professionals treating patients under GC therapy and develop guidelines for the prevention and treatment of GIO in postmenopausal women and men aged ≥50 years. The goal is to identify patients at very high and high

risk of fragility fractures or those with fragility fractures. The expert panel considered PICO questions related to different clinical scenarios and the recommendations were based on the voting panel's expertise, assessment of antifracture efficacy, and potential adverse events.

In patients with recent fragility fractures or multiple fragility fractures independently of BMD, or in those patients with a T-score ≤1.7, experts recommend treatment according to each clinical case, type of fracture, and risk of fracture. For the treatment algorithm, this expert panel recommends fracture risk stratification according to FRAX tool beyond the limitations explained previously. In patients with high risk or very high risk of fracture, zoledronate, denosumab, or teriparatide was recommended as the first option of treatment according to each clinical scenario and drug contraindications. Although romosozumab has been recently approved for severe osteoporosis in postmenopausal women, there is not enough evidence to be included here on patients under GC therapy. On the other hand, for those patients with T-score ≤ −1.7 without fragility fracture (moderate risk of fracture), oral bisphosphonates were recommended as the first option of treatment in most clinical situations, except contraindications, intolerance, or poor adherence. The use of a T-score of −1.7 as the threshold for intervention treatment[62] was defined after a systematic review analysis of previous studies,[57,58,72,73] indicating that more than 80% of the T-scores that discriminate between fractured and nonfractured were between −1.6 and −2.0. Although few studies have shown a T-score between −1.5 and −1.6 as a threshold of fracture, the use of a T-score value of −1.5 would lead to overtreatment of our study population.

The supplementation with calcium, vitamin D, physical exercise, and lifestyle modifications are essential as adjunct therapy. This panel of experts recommends the measurement of plasma levels of vitamin D before its supplementation and emphasizes the importance of performing bone densitometry by DXA at baseline or during the first month of GC therapy and annually while patients persist under GC therapy or persist under GIO treatment.

As a strength, this guideline presents 17 recommendations and 8 general principles developed using the GRADE methodology. In addition, recommendations about management, prevention, and therapeutical approaches in postmenopausal women and men aged ≥50 years under GC therapy are provided. However, some limitations are those areas this guideline does not cover, such as patients with organ transplants, those with stage 4–5 chronic kidney disease, or under inhaled GC therapy. Premenopausal women and men aged <50 years, patients under high GC doses or bolus, and pediatric population will be described in their respective guidelines.

CONCLUSIONS

This Argentine Guidelines for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis in Postmenopausal Women and Men Aged 50 Years and older provide evidence-based guidance for health care providers treating patients.

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