Recommendations

2014 update of recommendations on the prevention and treatment of glucocorticoid-induced osteoporosis

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\textbf{ABSTRACT}

\textbf{Objectives:} To update the recommendations on the prevention and treatment of glucocorticoid-induced osteoporosis issued in 2003 by the French National Authority for Health (HAS). This update was performed under the aegis of the Bone Section of the French Society for Rheumatology (SFR) and Osteoporosis Research and Information Group (GRIO), in collaboration with four French learned societies (primary-care, gastroenterology, internal medicine, and nephrology).

\textbf{Methods:} A task force composed of members of the medical specialties involved in managing patients with glucocorticoid-induced osteoporosis conducted a systematic literature review according to the method developed by the HAS then used the results to develop updated recommendations.

\textbf{Results:} These recommendations are intended for all physicians involved in the management of patients who are scheduled to start, or are taking, long-term glucocorticoid therapy (≥3 months) in any dose and for any reason. In postmenopausal women and men older than 50 years of age, treatment is warranted in the presence of any of the following risk factors for fracture: history of bone fragility fracture after 50 years of age, bone mineral density T-score ≤−2.5 at one or more sites, age ≥70 years, and dosage ≥7.5 mg/d prednisone-equivalent for longer than 3 months. Bisphosphonates can be used in all these situations; teriparatide can be given as first-line therapy in patients at high fracture risk but is reimbursed by the French statutory health insurance system only in patients having two or more prevalent vertebral fractures. The fracture risk is lower in nonmenopausal women and in men younger than 50 years of age, in whom treatment decisions should rest on a case-by-case evaluation.

\textbf{Conclusion:} These recommendations are intended to clarify the pharmacological management of glucocorticoid-induced osteoporosis.

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1. Introduction

The prevalence of glucocorticoid exposure in the general population is high, about 1% overall and up to 4.5% among postmenopausal women [1–4]. The most common diagnoses leading
to long-term glucocorticoid therapy are joint diseases (rheumatoid arthritis [RA], polymyalgia rheumatica [PMR], and connective tissue diseases), lung diseases (asthma and chronic obstructive pulmonary disease [COPD]), and chronic inflammatory bowel disease (IBD) [3]. A study of The Health Improvement Network (THIN) database on 4.5 million adults in the UK showed a 30% increase in the annual prevalence of glucocorticoid therapy over the 20-year enrolment period, with differences across underlying diagnoses [3]. Thus, the use of glucocorticoid therapy decreased among patients with asthma, COPD, or Crohn’s disease; remained stable in those with ulcerative colitis; and increased in patients with RA or PMR [3]. However, the prevalence of new prescriptions of long-term glucocorticoid therapy for RA decreased over time, suggesting changes in treatment practices related to the introduction of new drugs such as biological agents [3].

Glucocorticoid exposure is the leading cause of secondary osteoporosis and the most common cause of osteoporosis in young adults [5]. Although effective osteoporosis drugs are available, they are used for osteoporosis prevention in only a minority of patients exposed to long-term glucocorticoid therapy. Oddly enough, concomitant risk factors for osteoporosis (large number of comorbidities and concomitant treatments), which increase the need for prevention, are the factors most often associated with failure to prescribe preventive therapy [6–10]. Nevertheless, studies have documented increases in the prescription of bisphosphonates for patients receiving long-term glucocorticoid therapy in The Netherlands (54% in 2005 versus 38% in 2001; P=0.001), as well as in Denmark in patients with COPD [10,11]. Data obtained in France showed that only 30% of postmenopausal women taking long-term oral glucocorticoid therapy in dosages ≥7.5 mg/d of prednisone-equivalent were given bisphosphonate therapy in 2007, and this proportion was not higher in 2010 [12]. No data from France are available on the frequency and time trends of bisphosphonate therapy in patients with other inflammatory diseases.

### 2. Objectives and methods

These recommendations are intended for all physicians involved in the prevention and treatment of osteoporosis induced by long-term (≥3 months) exposure to glucocorticoid therapy in any dosage and for any reason. Recent data establish that glucocorticoid replacement therapy is not associated with bone loss [13].

These recommendations review the principles of pharmacological therapy for glucocorticoid-induced osteoporosis in the light of current indications, efficacy, and safety. They indicate treatment strategies appropriate for each clinical situation. Their objective is to improve the quality of care delivered to patients on long-term glucocorticoid therapy, in order to decrease the risk of fracture. The content of these recommendations was discussed, written, and validated according to the method developed by the French National Authority for Health (HAS). They were drafted by a project manager and scientific committee then discussed and revised by a multidisciplinary review committee. When published data were insufficient or incomplete, the recommendations were developed by professional consensus, based on current practice and expert opinion. The recommendations recently issued by the American College of Rheumatology (ACR), International Osteoporosis Foundation (IOF), and European Calcified Tissue Society (ECTS) [14,15] were analyzed and discussed during the professional consensus process. The recommendations in this article cannot deal with every possible situation, for instance in terms of specific clinical cases, comorbidities, and inpatient care protocols. They do not presume to cover all possible management strategies. In no case can they be interpreted as taking the place of each physician’s individual responsibility toward his or her patients.

**Fig. 1. Pathophysiology of glucocorticoid-induced osteoporosis.**

The following learned societies contributed to the revision of the initial draft of the recommendations: National Organization of Teaching Primary-Care Physicians (Collège National des Généralistes Enseignants [CNGE]), Osteoporosis Research and Information Group (Groupe de Recherche et d’Information sur les Ostéoporoses [GRIO]), French National Society for Gastroenterology (Société Nationale Française de Gastroentérologie [SNFGE]), French National Society for Internal Medicine (Société Nationale Française de Médecine Interne, SNFMI), Nephropathy Society (Société de Néphrologie), and French Society for Rheumatology (Société Française de Rhumatologie [SFR]).

### 3. Impact of glucocorticoid therapy on bone

#### 3.1. Pathophysiology of glucocorticoid-induced osteoporosis

Glucocorticoids in pharmacological dosages exert adverse effects on bone-tissue via both direct and indirect mechanisms [16–18] (Fig. 1). They directly alter bone cell metabolism. Their indirect effects are mediated by a variety of mechanisms including decreased intestinal absorption of calcium, increased urinary excretion of calcium, glucocorticoid-induced hypogonadism, and glucocorticoid-induced myopathy responsible for an increased risk of falls [17]. The main net effect is inhibition of bone formation combined with uncoupled excessive bone resorption. These effects occur against a background of bone-tissue turnover alterations due to the inflammatory disease for which glucocorticoid therapy is prescribed. Chronic inflammation is also a cause of increased bone resorption and bone loss. The rapid decrease in bone strength seen early after glucocorticoid treatment initiation is thus ascribable to a marked decrease in bone formation against a background of altered bone turnover with increased bone resorption.

#### 3.2. Bone loss due to glucocorticoid therapy

Glucocorticoid-induced bone loss is detectable early, within 6 months of treatment onset. A 2002 meta-analysis of 56 cross-sectional and 10 longitudinal studies showed 2% to 3% of bone loss within the first treatment year at both the lumbar spine and the femur [19]. Analyses of data from the placebo groups of therapeutic trials reported during the same period confirm these data [20,21]. The amount of bone lost depends on the glucocorticoid dosage and treatment duration [22,23]. It also varies within a given population, and no absorptiometry, biological, or clinical criteria are available for predicting the occurrence and severity of bone loss. In the meta-analysis, the main reasons for glucocorticoid therapy were rheumatic diseases (67%), followed by COPD (16%) [19]. It is worth noting that these data were obtained over a decade ago. Few studies have investigated the time-course of bone mineral density.
(BMD) values in patients with inflammatory joint disease receiving biological agents, which are more effective than previously available drugs. Two studies in patients with RA taking low-dose glucocorticoid therapy and biotherapies to achieve optimal control of the inflammatory process found no evidence of bone loss [24,25].

3.3. Risk of fracture associated with glucocorticoid therapy

A 30% to 50% increase in the fracture risk has been documented in patients receiving long-term glucocorticoid therapy in both cross-sectional and longitudinal studies [26,27]. The fracture risk was dose-dependent: although apparent even at the lowest doses, the increase was chiefly noticeable with doses greater than 7.5 mg/d of prednisone-equivalent. Fractures occurred 3 to 6 months after treatment initiation and decreased in frequency as early as 3 months after treatment discontinuation in large population-based studies [26,27]. Glucocorticoid therapy initiation within the past 12 months with a treatment duration longer than 90 days was associated with a decrease in femoral neck BMD and with increases in the risk of major fractures (5.4% vs. 7.7%; relative risk [RR], 1.25; 95% confidence interval [95%CI], 1.07–1.45; P = 0.004) and hip fractures (1.1% vs. 1.8%; RR, 1.61; 95%CI, 1.18–2.20; P = 0.003) independently from the BMD values [28]. In this study, neither glucocorticoid therapy for 12 months or longer nor glucocorticoid therapy for less than 90 days was associated with an increase in the fracture risk [28]. A study involving routine radiographs of the thoracic and lumbar spine in postmenopausal women taking long-term glucocorticoid therapy and reporting no back pain showed that the prevalence of vertebral fractures was higher than expected and that this increase could not be ascribed solely to the dose and duration of glucocorticoid therapy [29]. The analgesic effect of glucocorticoids may explain the greater frequency of undiagnosed vertebral fractures. An increased risk of vertebral fracture has been documented in a variety of chronic diseases including COPD and asthma, in which thoracic kyphosis due to vertebral fractures can result in a restrictive syndrome that worsens the respiratory impairments.

3.4. Influence of the route of administration

Published data suggest that topical glucocorticoid therapy administered nasally or transcutaneously may have little or no effect on the fracture risk. The increased fracture risk in patients taking inhaled glucocorticoid therapy is usually related to the underlying disease (and therefore to the inflammatory process) and concomitant oral glucocorticoid therapy. However, inhaled glucocorticoid therapy in a daily dosage ≤ 7.5 mg prednisone-equivalent may cause a slight increase in the fracture risk [30]. Available data about potential effects of high-dose intravenous glucocorticoid therapy given for short periods are conflicting and do not allow definite conclusions.

3.5. Limitations of available data

Most studies focused on patients with joint diseases or respiratory diseases (asthma and COPD). Patients with other chronic inflammatory diseases such as chronic IBD (Crohn’s disease and ulcerative colitis) are underrepresented in clinical studies. No convincing evidence has been obtained that the cumulative glucocorticoid dose correlates with the fracture risk, perhaps because self-medication and recall bias adversely affect the accuracy of cumulative dose estimates. Epidemiological studies cannot separate the role for bone inflammation from that of glucocorticoid exposure. Except in RA, few recent data are available on the risk of bone loss and fracture in patients taking biological agents in combination with systemic glucocorticoid therapy. Biological agents (TNFα antagonists) are associated with increases in BMD values but have not been proven to decrease the fracture risk [31,32].

4. Risk factors for fracture in patients taking long-term glucocorticoid therapy

4.1. History of fracture

A previous peripheral fracture is the strongest risk factor for vertebral fractures in patients with RA [33]. As indicated above, the frequency of prevalent vertebral fractures is underestimated due to the mildness of the symptoms, which is probably attributable to the analgesic effect of glucocorticoids.

4.2. Risk factors related to patient characteristics

In addition to glucocorticoid exposure, a number of patient characteristics may influence the fracture risk. Characteristics that are relevant in both males and females include age, risk factors for falls, concomitant medications, comorbidities, and the status of the underlying disease. In women, the menopause and the duration of estrogen deprivation also influence the fracture risk. Among women taking long-term glucocorticoid therapy, those aged 60 to 80 years had a 26-fold increase in the risk of vertebral fractures compared to those aged 18 to 31 years after adjustment for alcohol and tobacco use and for the starting and cumulative glucocorticoid doses [34]. In contrast, nonmenopausal women and men younger than 50 years of age are at low risk for fractures [35]. Although epidemiological studies show an increased risk compared to the same-age general population, regardless of the glucocorticoid dose [26], the risk remains low in these groups. Thus, in trials of the efficacy of etidronate, risedronate, and alendronate in the treatment of glucocorticoid-induced osteoporosis, a single fracture was recorded in the 157 nonmenopausal women treated with the placebo [20,21,36,37]. However, the women included in these studies had a low fracture risk with normal baseline BMD values and, consequently, the results are not applicable to all patients, most notably those with preexisting bone loss. It is important to note that patients with chronic inflammatory diseases requiring glucocorticoid therapy often have several independent risk factors for fractures [38]. For instance, patients with RA often have not only chronic inflammation and chronic glucocorticoid therapy as risk factors, but also a low body mass index and an increased risk of falls [39].

4.3. Bone mineral density (BMD) values

BMD values are more difficult to interpret in patients with long-term glucocorticoid exposure compared to postmenopausal women, since fractures are more common during glucocorticoid therapy than expected based on absolute BMD values or changes in BMD values over time [40]. Furthermore, in contrast to studies of postmenopausal osteoporosis, therapeutic trials in glucocorticoid-induced osteoporosis were performed in patients selected based on the use of glucocorticoids, as opposed to baseline BMD values.

4.4. FRAX® score in glucocorticoid-induced osteoporosis

The FRAX® tool was introduced in 2008 by the World Health Organization to quantify the absolute 10-year risk of major fractures in individuals older than 40 years of age (www.sheffield.ac.uk/FRAX) [41]. Data from 12 international cohorts including about 60,000 individuals in all were used to identify risk factors and to evaluate their predictive value. Glucocorticoid therapy for longer than 3 months was among the risk factors selected to build the FRAX® tool. The other risk factors were
age, body mass index, history of fracture, hip fracture in one or both parents, current smoking, RA and other causes of secondary osteoporosis, alcohol abuse, and BMD at the femoral neck. The FRAX® tool, which is available online, provides the 10-year likelihood of sustaining a hip fracture or a major fracture (hip fracture, humeral fracture, wrist fracture, and clinical vertebral fracture). The many limitations of the FRAX® tool include failure to take into account the dose, duration, and period of administration of glucocorticoid therapy; and use of BMD at the femoral neck, whereas bone loss during glucocorticoid therapy predominates at the spine.

The 2010 update of the international ACR recommendations and the 2012 guidelines issued by the IOF/ECTS incorporate use of the FRAX® tool within the treatment strategy [14,15]. It has been suggested that the FRAX® score should be adjusted for the daily glucocorticoid dose [42,43] if < 2.5 mg or > 7.5 mg of prednisone-equivalent.

5. Recommended strategies for preventing and treating glucocorticoid-induced osteoporosis

5.1. Fracture risk evaluation in patients taking, or scheduled to take, long-term glucocorticoid therapy

Given the rapid onset of bone loss and early fracture risk increase after glucocorticoid therapy initiation, a baseline evaluation of the fracture risk is recommended in all patients starting oral glucocorticoid therapy expected to last longer than 3 months; in the absence of a baseline evaluation, the fracture risk should be evaluated in patients on oral glucocorticoid therapy (Grade A). This evaluation is recommended regardless of the glucocorticoid dosage (Grade A). The identification of patients at high risk for fractures relies on a multifactorial evaluation that takes into account the characteristics of the patient, underlying inflammatory disease, and glucocorticoid regimen.

5.1.1. Assessment for previous fractures

The detection of previous low-energy fractures is a crucial component of the fracture risk evaluation, as such fractures constitute the strongest risk factor for further fractures (Grade A). Radiographs of the spine should not be obtained routinely but are indicated in patients with height loss \( \geq 4 \) cm compared to the reported height at 20 years of age, height loss \( \geq 2 \) cm compared to height measured during follow-up, or back pain. Dual-photon X-ray absorptiometry machines can be used for a morphological assessment designed to detect vertebral fractures (Vertebral Fracture Assessment [VFA]). The radiation dose is sufficiently low to allow the routine use of this investigation at glucocorticoid therapy initiation and in patients who have been taking \( \geq 7.5 \) mg/d of prednisone-equivalent for longer than 3 months [44] (Grade B).

5.1.2. Bone mineral density (BMD) measurement

BMD measurement is recommended in all patients starting oral glucocorticoid therapy and in those who have been taking oral glucocorticoid therapy for longer than 3 months in the absence of baseline BMD measurement, regardless of the glucocorticoid dose (Professional consensus). The French statutory healthcare system reimburses BMD measurement for patients expected to require expected oral glucocorticoid therapy for longer than 3 consecutive months in a dose \( \geq 7.5 \) mg/day of prednisone-equivalent. In young adults, the T-score can be used instead of the Z-score, since the two are equivalent in this age group. In patients on long-term glucocorticoid therapy, BMD measurement is not sufficient to predict the fracture risk, and a decrease in BMD values alone is usually not sufficient reason to start osteoporosis drug treatment [45].

5.1.3. FRAX® score determination

Determination of the FRAX® score is not useful when osteoporosis drug treatment is obviously indicated (Professional consensus). Use of the FRAX® tool has not been validated in individuals younger than 40 years of age and is therefore not recommended in non-menopausal women or men younger than 50 years of age (Grade A). Determination of the adjusted FRAX® score is useful in other patient groups (Professional consensus). No FRAX® score cutoff for determining when treatment is in order has been validated in glucocorticoid-induced osteoporosis. The score found in same-age women having a history of fracture is therefore an acceptable cutoff (Fig. 2) (Professional consensus).

5.1.4. Measurement of bone turnover markers

No convincing evidence exists that measuring markers for bone turnover (bone formation and resorption) is helpful in glucocorticoid-induced osteoporosis. The use of these markers for predicting the fracture risk is not recommended (Grade A).

5.2. Therapeutic prerequisites

5.2.1. General measures

These measures are essential (Table 1). The best prevention is administration of the minimal effective dosage of glucocorticoid (Professional consensus):

- the glucocorticoid dose should be evaluated at each visit;
- all available glucocorticoid-sparing methods should be used (e.g., administration by intraarticular injection or inhalation);

<table>
<thead>
<tr>
<th>Table 1</th>
<th>General principles of the management of glucocorticoid-induced osteoporosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendations</strong></td>
<td><strong>Level of evidence</strong></td>
</tr>
<tr>
<td>Determine the minimal effective glucocorticoid dose</td>
<td>C</td>
</tr>
<tr>
<td>Use all possible glucocorticoid-sparing options</td>
<td>C</td>
</tr>
<tr>
<td>Consider alternative routes of glucocorticoid administration (topical administration, inhalation)</td>
<td>C</td>
</tr>
<tr>
<td>Ensure adequate intakes of calcium (preferably via a balanced diet) and vitamin D</td>
<td>C</td>
</tr>
<tr>
<td>Encourage regular physical activity</td>
<td>C</td>
</tr>
<tr>
<td>Encourage smoking cessation and a decrease of excessive alcohol use to a reasonable level</td>
<td>C</td>
</tr>
<tr>
<td>Take fall prevention measures, most notably in elderly patients</td>
<td>A</td>
</tr>
</tbody>
</table>

• effective disease-modifying antirheumatic drugs should be given to control the inflammation and the course of the underlying disease;
• every effort should be made to eliminate other identified risk factors for osteoporosis, including other causes of bone loss;
• the fall risk should be minimized: preventive measures advocated to prevent falls in elderly individuals (e.g., fall-proofing the home, engaging in physical activity programs, correcting visual deficiencies, and adjusting antihypertensive and hypnotic medications) are effective in preventing falls and fractures (Grade A) [46].

5.2.2. Calcium intake
Calcium and vitamin D supplements are widely prescribed in patients given glucocorticoid therapy, based on pathophysiological considerations and in the absence of scientific evidence to support this practice. Calcium and vitamin D supplementation in physiological dosages did not prevent the occurrence of bone loss and fractures in the placebo groups of large therapeutic trials [20,21,36,37]. The French National Nutrition for Health Program (PNSS) recommends a daily calcium intake of 800 to 1200 mg, which requires four helpings per day of dairy products (e.g., yoghurt, fresh cheese, fermented milk, cheese, and/or milk). There is some evidence to suggest that calcium supplementation may increase the risk of cardiovascular events in elderly women [47–49]. This effect was chiefly found in individuals whose daily calcium intake from food was adequate [50]. Furthermore, no increase in cardiovascular events was demonstrated in a large study of elderly women given supplemental calcium or a placebo [51]. Compensating an inadequate dietary calcium intake diminishes the risk factors associated with bone loss. The calcium intake should be evaluated using a food frequency questionnaire (Appendix 1 in the online supplement). Routine prescription of calcium supplements is not recommended (Grade A).

5.2.3. Vitamin D intake
Given the risk of bone loss due to both the underlying inflammatory disease and glucocorticoid therapy [52], a serum 25-OH vitamin D assay should be performed (Grade A). The serum level of 25-OH vitamin D should be maintained at the optimal value, which has been set at 30 ng/mL (75 nmol/L) [52] based on findings from molecular and clinical studies that did not focus specifically on glucocorticoid-induced osteoporosis (Grade A). Given this treatment objective, the 25-OH vitamin D assay should be repeated once to allow adjustment of the loading and maintenance doses of supplemental vitamin D (Grade B).

In patients with vitamin D insufficiency or deficiency, a loading dose of vitamin D should be given to elevate the serum 25-OH vitamin D level above the target of 30 ng/mL (Grade A). The following dosages are suggested [52]:

- in patients with vitamin D deficiency (serum 25-OH vitamin D < 10 ng/mL), four oral doses of 100,000 IU each, taken at intervals of 2 weeks;
- in patients with marked vitamin D insufficiency (serum 25-OH vitamin D, 10 to 20 ng/m), three oral 100,000 IU doses each, taken at intervals of 2 weeks;
- in patients with mild vitamin D insufficiency (serum 25-OH vitamin D, 20 to 30 ng/mL), two oral 100,000 IU doses each, taken at intervals of 2 weeks.

The maintenance dose is 800 to 1200 IU/day (or the equivalent of 100,000 IU every 2–3 months). The currently available data do not support the use of high-dose vitamin D supplementation (500,000 or 600,000 IU once or twice every year) [53] (Grade A). Dihydroxy-vitamin D derivatives are not recommended, in particular because they carry a risk of increased urinary calcium excretion (Grade A).

5.3. Treatment of postmenopausal women and men older than 50 years of age
The suggested strategy for preventing bone loss and fractures is tailored to each individual patient. Osteoporosis medications have been proven effective in preventing bone loss and decreasing the vertebral fracture rate in studies providing variable levels of evidence (Table 2) [54–60]. No proof of efficacy in decreasing the risk of nonvertebral fractures has been obtained. The same recommendations are appropriate for men older than 50 years and postmenopausal women based on evidence demonstrating that the cost/efficacy ratio of interventions for glucocorticoid-induced osteoporosis in men older than 50 years is similar to that in postmenopausal women having a comparable fracture risk [61,62].

5.3.1. Indications for osteoporosis medications
Postmenopausal women and men older than 50 years of age should be considered at high risk for fractures and therefore eligible for osteoporosis drug therapy if they meet the following criteria (Grade B) (Fig. 3):

- history of bone frailty fracture after 50 years of age;
- T-score ≤ −2.5 at the lumbar spine and/or femur;
- age ≥ 70 years, since in this age group FRAX® scores evaluating the fracture risk are similar in women starting glucocorticoid therapy and in women with a history of fracture;
- long-term high-dose glucocorticoid therapy (> 7.5 mg/d prednisone-equivalent for longer than 3 months); selection of this dose cutoff is based on its use in most clinical trials as an inclusion criterion and on epidemiological data showing that the relative risk of vertebral fracture increases from 2.6 with doses of 2.5 to 7.5 mg/d to 5.2 with doses > 7.5 mg/d [26].

In all other situations, decisions should be based on the FRAX® score adjusted for the glucocorticoid dose, if needed after obtaining advice from a bone diseases specialist (Fig. 3) (Professional consensus). Patients who are not eligible for osteoporosis drug therapy (with a bisphosphonate or teriparatide) should receive the general measures described above and undergo follow-up BMD measurement, usually after 1 year, although this interval may be adjusted based on the initial BMD values and glucocorticoid dose (Professional consensus). When the follow-up BMD measurement shows...
Table 2

<table>
<thead>
<tr>
<th>Study drug (StDr)</th>
<th>Comparator (Co)</th>
<th>Patients (n)</th>
<th>Type of intervention</th>
<th>Duration</th>
<th>Lumbar change (%)</th>
<th>Hip (femoral neck or total hip)</th>
<th>Vertebral fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etidronate [54]</td>
<td>PBO</td>
<td>117</td>
<td>Prev</td>
<td>1 year</td>
<td>+0.3</td>
<td>−2.79</td>
<td>4/59 (7%)</td>
</tr>
<tr>
<td>Etidronate [55]</td>
<td>PBO</td>
<td>141</td>
<td>Prev</td>
<td>1 year</td>
<td>+0.61</td>
<td>−3.23</td>
<td>5/58 (9%)</td>
</tr>
<tr>
<td>Risedronate [20]</td>
<td>PBO</td>
<td>224</td>
<td>Prev</td>
<td>1 year</td>
<td>+0.6</td>
<td>−2.8</td>
<td>3/53 (5.7%)</td>
</tr>
<tr>
<td>Risedronate [21]</td>
<td>PBO</td>
<td>290</td>
<td>Cur</td>
<td>1 year</td>
<td>+2.9</td>
<td>+0.4</td>
<td>3/60 (5%)</td>
</tr>
<tr>
<td>Risedronate [56]</td>
<td>PBO</td>
<td>518</td>
<td>Prev + Cur</td>
<td>1 year</td>
<td>+1.9</td>
<td>−1</td>
<td>6/111 (5.4%)</td>
</tr>
<tr>
<td>Alendronate [31]</td>
<td>PBO</td>
<td>477</td>
<td>Prev</td>
<td>1 year</td>
<td>+3.1</td>
<td>−0.6</td>
<td>8/268 (2.9%)</td>
</tr>
<tr>
<td>Alendronate [32]</td>
<td>PBO</td>
<td>477</td>
<td>Cur</td>
<td>2 years</td>
<td>+3.9</td>
<td>−0.8</td>
<td>1/143 (0.7%)</td>
</tr>
<tr>
<td>Zoledronic acid [57]</td>
<td>Risedronate</td>
<td>545</td>
<td>Cur</td>
<td>1 year</td>
<td>+4.1</td>
<td>+2.7</td>
<td>3/833 (3%)</td>
</tr>
<tr>
<td>Zoledronic acid [57]</td>
<td>Risedronate</td>
<td>288</td>
<td>Prev</td>
<td>1 year</td>
<td>+2.6</td>
<td>+2.0</td>
<td>−9/26 (3.4%)</td>
</tr>
<tr>
<td>Zoledronic acid [58]</td>
<td>Risedronate</td>
<td>Data for 245</td>
<td>Cur + Prev</td>
<td>1 year</td>
<td>+2.5</td>
<td>−0.2</td>
<td>9/169 (5.3%)</td>
</tr>
<tr>
<td>Teriparatide [59]</td>
<td>Alendronate</td>
<td>428</td>
<td>Cur</td>
<td>1.5 years</td>
<td>+2.0</td>
<td>+0.4</td>
<td>1/165 (0.6%)</td>
</tr>
<tr>
<td>Teriparatide [60]</td>
<td>Alendronate</td>
<td>428</td>
<td>Cur</td>
<td>3 years</td>
<td>+2.0</td>
<td>+1.0</td>
<td>2/133 (1.5%)</td>
</tr>
</tbody>
</table>

BMD: bone mineral density; RR: relative risk; 95%CI: 95% confidence interval; PBO: placebo; Prev: preventive treatment; Cur: curative treatment.

Table 3

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Licensed indications</th>
<th>Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTONEL® 5 mg, tablets</td>
<td>Bone mass preservation or increase in postmenopausal women requiring systemic</td>
<td>Same as license</td>
</tr>
<tr>
<td>(etidronate)</td>
<td>glucocorticoid therapy for longer than 3 months in doses ≥ 7.5 mg/d prednisone-equivalent</td>
<td></td>
</tr>
<tr>
<td>DIDRONEL® 400 mg, tablets</td>
<td>Prevention of bone loss in patients requiring systemic glucocorticoid therapy for</td>
<td>Not reimbursed</td>
</tr>
<tr>
<td>(etidronate)</td>
<td>longer than 3 months in doses &gt; 7.5 mg/d prednisone-equivalent</td>
<td></td>
</tr>
<tr>
<td>FOSAMAX® 5 mg, tablets</td>
<td>Prevention of bone loss in patients requiring systemic glucocorticoid therapy for</td>
<td>Not reimbursed</td>
</tr>
<tr>
<td>(etidronate)</td>
<td>longer than 3 months in doses &gt; 7.5 mg/d prednisone-equivalent</td>
<td>Dosage not available in France</td>
</tr>
<tr>
<td>ACLAISTA 5 mg en intravenous</td>
<td>Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy</td>
<td>Same as license</td>
</tr>
<tr>
<td>(etidronate)</td>
<td>in postmenopausal women and men at high risk for fractures</td>
<td></td>
</tr>
<tr>
<td>FORSTEO 20 µg subcutaneous</td>
<td>Treatment of glucocorticoid-induced osteoporosis in women and men at high risk for</td>
<td>If at least two prevalent</td>
</tr>
<tr>
<td>injection (teriparatide)</td>
<td>fractures who are taking long-term systemic glucocorticoid therapy</td>
<td>vertebral fractures, for</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18 months of use</td>
</tr>
</tbody>
</table>

Etidronate 400 mg and alendronate 5 mg are no longer marketed in France.


5.3.2. Selection of the osteoporosis drug

Among bisphosphonates, zoledronic acid or risedronate is always an appropriate choice (Grade B) [20,21,36,37,56–58,63] (Tables 2 and 3). Alendronate is not available in France in the licensed dosage (5 mg/d). Teriparatide can be prescribed as the first-line drug in patients at high fracture risk and is reimbursed by the French statutory healthcare system in patients with at least two prevalent vertebral fractures at diagnosis [59,60] (Grade A).

5.4. Treatment of nonmenopausal women and men younger than 50 years of age

In nonmenopausal women and men younger than 50 years of age, the fracture risk is lower and treatment decisions are rendered difficult by the paucity of data on the efficacy of osteoporosis drugs in this population and by the risks associated with bisphosphonate therapy in women who subsequently become pregnant.

As for all these recommendations, osteoporosis drug therapy should be given to patients with established bone frailty documented by a history of low-energy fracture (Professional consensus). The use of bisphosphonates in this indication is off-label. Teriparatide is reimbursed in France under the same conditions as described above. Osteoporosis drug therapy should not be given routinely to patients without a history of low-energy fracture. Instead, the treatment decision should rely on an evaluation of the severity of the underlying disease, glucocorticoid dose, expected treatment duration, and BMD values (Professional consensus). Nonmenopausal women who take osteoporosis drugs should use an effective birth control method. When bisphosphonates are used off-label, preference should be given to a bisphosphonate with a limited carry-over effect (risedronate) (Professional consensus). Women should be advised against starting a pregnancy during the treatment and within 6 months after its discontinuation.

5.5. Duration of osteoporosis drug therapy

The short duration of available therapeutic trials precludes conclusions regarding the optimal treatment duration...
The duration of clinical experience with drugs used to treat glucocorticoid-induced osteoporosis is 2 years for bisphosphonates and 36 months for teriparatide (which is reimbursed only for the first 18 months and licensed for a maximum duration of 2 years). Continued therapy beyond these durations should be reevaluated on a case-by-case basis every 2 years (Professional consensus). In postmenopausal women started on osteoporosis drug therapy because of a bone frailty fracture or BMD values within the osteoporosis range, the recommended duration of the first treatment sequence is 3 to 5 years, and the criteria for stopping or continuing osteoporosis drug therapy in patients with postmenopausal osteoporosis should be applied. The appropriateness of prescribing osteoporosis drug therapy for longer than 5 years should be evaluated. This evaluation does not necessarily require discontinuation of the drug.

6. Patient follow-up

6.1. Evaluation of treatment adherence

As with all drugs used to treat chronic conditions, osteoporosis drugs are effective only when taken as ordered. Several studies have shown that poor treatment adherence translates into decreased efficacy. Clinical follow-up may be sufficient to assess adherence (Professional consensus).

6.2. Role for bone mineral density (BMD) measurement during follow-up

Given the rapid onset of bone loss, annual BMD measurement is recommended during the first 2 years of glucocorticoid therapy in the absence of osteoporosis drug therapy or at the end of an osteoporosis drug sequence. Subsequently, the frequency of BMD measurement should be determined based on the BMD values, glucocorticoid dose, and level of control of the underlying disease (Professional consensus).

6.3. Role for bone turnover markers

Assays of markers for bone turnover (bone formation and resorption) have not been proven useful for monitoring osteoporosis drug therapy in patients with glucocorticoid-induced osteoporosis. As with the treatment of postmenopausal osteoporosis, these assays may be performed to document the pharmacological effect of bisphosphonates and to assess patient adherence (Professional consensus).

6.4. Other treatment monitoring methods

The other methods are:

- height measurement once a year: vertebral fractures result in height loss, which is a nonspecific sign of vertebral disease (Professional consensus);
- a morphological assessment of the spine (radiographs, VFA) is indicated in patients with back pain or height loss ≥ 2 cm during follow-up (Professional consensus).

6.5. Criteria for stopping osteoporosis drug therapy

Osteoporosis drug discontinuation can be considered in patients who meet all the following criteria (Professional consensus): no fracture during treatment AND prednisone-equivalent dose ≤ 7.5 mg/d AND no new risk factors AND optimal control of underlying disease activity AND no change in BMD values (with change defined as a decrease ≥ 0.03 g/cm² at one or both sites). In every case, the decision to stop osteoporosis drug therapy should rest on a case-by-case evaluation of the risk/benefit ratio.

6.6. Failure of osteoporosis drug therapy

No data are available on switching or combining osteoporosis drugs in patients with significant bone loss (BMD decrease ≥ 0.03 g/cm²) or bone frailty fractures during combined long-term glucocorticoid therapy and osteoporosis drug therapy. Advice from a bone diseases specialist should ideally be obtained (Professional consensus).

7. Safety of osteoporosis drugs

Clinical trials in glucocorticoid-induced osteoporosis included fewer patients and involved shorter follow-ups compared to studies of postmenopausal osteoporosis. Thus, few data are available on patients given long-term osteoporosis drug therapy. The safety profiles of bisphosphonates and teriparatide seem comparable to those seen in postmenopausal osteoporosis. Patients treated with bisphosphonates should be informed of the very small risk of jaw osteonecrosis and atypical femoral fracture. Appropriate dental care should be provided at treatment initiation but should not delay the initiation of bisphosphonate therapy in patients at high risk for fractures. As recommended in the general population, oral and dental health should be evaluated at least once a year. Dental extractions can be performed when necessary, under antibiotic therapy. Bisphosphonate therapy for osteoporosis does not contraindicate dental implants or oral surgery (recommendations issued by the French Society for Stomatoloy, Maxillofacial Surgery, and Oral surgery, www.sfcmfco.fr). An increased risk of atypical femoral fracture has been reported in patients receiving glucocorticoid therapy or bisphosphonate therapy, and this risk may increase with the duration of bisphosphonate exposure. Atypical femoral fractures are usually heralded by several weeks or months of thigh pain. Very few cases have been reported. The available data do not challenge the favorable risk/benefit ratio of osteoporosis drug therapy in patients at risk for osteoporosis but should be taken into account when considering the appropriateness of long-term bisphosphonate therapy in patients receiving long-term glucocorticoid therapy (Professional consensus).

Disclosure of interest

K. B.: occasional interventions: fees for work as an expert or speaker for Amgen, Lilly, MSD, Novartis, and Servier; indirect interests: funding for research programs and investigator fees from Lilly.

B. C.: occasional interventions: fees for work as an expert or speaker for Amgen, Ferrin, Lilly, Medtronic, MSD, Novartis, Roche Diagnostics, Rottapharm, and Servier; indirect interests: funding for research programs and investigator fees from Amgen, Novartis, and Servier.

C. R.: occasional interventions: fees for work as an expert or speaker for Amgen Lilly, MSD, Roche, Novartis, and Servier; indirect interests: funding for a nonprofit research organization from Bongrain, Amgen Lilly, MSD, and Servier.

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Servier, and Warner-Chilcott; indirect interests: funding for a non-profit research organization from Amgen, MSD, and Servier.

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T.T.: occasional interventions: fees for work as an expert or speaker for de Amgen, BMS, Chugai/Roche, Genévrier, Gibaud, GSK, Lilly, MSD, Novartis, Servier, and UCB; indirect interests: funding for research programs and investigator fees from Amgen, Chugai/Roche, MSD, Novartis, Pfizer, Servier, UCB, and Warner-Chilcott.

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Appendix A. Supplementary data

Supplementary data (Appendices 1 and 2) associated with this article can be found, in the online version, at http://www.sciencedirect.com and http://dx.doi.org/10.1016/j.jbspin.2014.10.001.

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