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CONSENSUS STATEMENT

Evidence-based guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis: a consensus document of the Belgian Bone Club

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Abstract Glucocorticoids (GCs) are frequently prescribed for various inflammatory and/or life-threatening conditions concerning many systems in the body. However, they can provoke many aftereffects, of which osteoporosis (OP) is one of the most crippling complications, with its host of fractures. The dramatic increase in bone fragility is mainly attributable to the GC-induced rapid bone loss in all skeletal compartments. We have reviewed the meta-analyses and randomized controlled studies reporting medical therapeutic interventions currently registered in Belgium for the management of GC-OP comparatively with a placebo. Based on this research, an expert meeting developed a consensus on the prevention and therapy of GC-OP. The pathophysiology of GC-OP is complex. Several factors, acting separately or synergistically, have been described. Their great number could help to understand the rapidity of bone loss and of bone fragility occurrence, indicating that a rapid therapeutic intervention should be implemented to avoid complications. All patients on GCs are threatened with OP, so the prevention and/or therapy of GC-OP should be considered not only for postmenopausal females, but also for osteopenic premenopausal females and for males put on a daily dose of at least 7.5 mg equivalent prednisolone that is expected to last at least 3 months. Non-pharmacological interventions, such as exercise and avoidance of tobacco and alcohol, should be recommended, even if their role is not definitely settled in GC-OP prevention. Supplemental calcium and vitamin D should be considered as the first-line therapy because of the decrease in intestinal calcium absorption provoked by GCs. They also could be considered either as isolated therapy in patients taking less than 7.5 mg prednisolone daily and/or for a predicted period shorter than 3 months or as adjuvant therapy to other more potent drugs. Hormone replacement therapy could be considered in young postmenopausal females on GC, such as in postmenopausal OP, or in men with low androgen levels. Calcitonin appears to have a protective effect on trabecular bone in GC-OP, just as in postmenopausal OP. There is an increasing body of evidence supporting the antifracture efficacy of bisphosphonates, notably alendronate and risedronate. Preventative and curative therapy of GC-OP should be maintained as long as the patient is on GC treatment

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and could be stopped after weaning from GC, because there is more than circumstantial evidence of some recovery of BMD when GCs are stopped. There is no indication in GC-OP for any combination of two antiresorptive agents (except for calcium and vitamin D) or for an antiresorptive and an anabolic agent. There is indeed no proof that the increased costs of combined treatments will translate into increased therapeutic efficacy.

Keywords DXA · Evidence-based · Guidelines · Osteoporosis · Therapy

Introduction

Glucocorticoids (GCs) are among the most frequently prescribed drugs because of their anti-inflammatory and immunosuppressive properties. Their therapeutic indications are widespread and concern nearly all of the medical specialties, dealing with conditions of various systems such as the skin, lung, hematologic, intestinal and renal, rheumatic diseases, as well as the organ transplantation domain. However, the side effects of GCs are commensurate with their great utility. They comprise, e.g., skin atrophy, moon face appearance, trunk obesity, cataracts, disturbances in glucose tolerance and lipid metabolism. This list is not limitative. The most crippling complication of GC therapy consists of secondary osteoporosis (OP), leading to enhanced frailty of the skeleton. Van Staa et al. estimated the relative risk of fractures among oral GC users to amount to 1.33 for non-vertebral fracture, to 1.61 for hip fracture and to 2.60 for vertebral fracture, respectively [1]. The relative risks increase proportionally to the dose, starting from 0.99 and 1.55 on a daily dose lower than 2.5 mg, increasing to 1.77 and 2.59 at doses between 2.5 and 7.5 mg and to 2.27 and 5.18 at doses of 7.5 mg or greater, respectively, for hip and vertebral fractures [1]. The dramatic increase in bone frailty is mainly attributable to the GC-induced rapid bone loss in all compartments of the skeleton [2, 3]. The aim of this paper is to achieve an evidence-based consensus about the prevention and therapy of GC-OP.

Materials and methods

Meta-analyses and randomized controlled trials (RCTs) comparing medical therapeutic interventions currently registered in Belgium for the management of GC-induced OP with a placebo were reviewed. The results had to report a follow-up of at least 1 year on either bone mineral density (BMD), radiological or clinical fractures. Thorough research in Medline for the period from 1966 to 2005, and in databases such as the Cochrane Controlled Register, was performed for retrieval of the relevant literature. Based on this extensive search, a critical appraisal of the data was obtained through a consensus experts' meeting.

Pathophysiology

The pathophysiology of GC-OP is particularly complex, for several factors have been indicated in its occurrence. All of them have probably not yet been elucidated completely. Both daily and cumulative GC doses as well as the treatment duration affect the incidence of GC-OP [4, 5]. The adverse effects of GC on the skeleton occur rapidly after the initiation of therapy, implying that they could be related more to daily than to cumulative doses [5, 6]. Moreover, it has been suggested that fractures in GC-treated patients could occur at higher bone mineral density (BMD) than in postmenopausal OP [6, 7]. This would imply that preventative measures should be implemented immediately after starting GC therapy. Furthermore, it should not be forgotten that the underlying condition justifying GC therapy could also be responsible per se for some bone loss, such as, e.g., rheumatoid arthritis [4]. Gender, menopausal status, age [8], peak bone mass prior to starting GC therapy, the variability of prednisolone clearance from the plasma [9] and the specificity of the GC-receptor haplotype [10] might also play a role in the rapidity of GC-OP development.

GCs provoke both a dramatic decrease in bone formation and a modest increase in bone resorption [11]. GCs might induce some degree of secondary hyperparathyroidism [12], and consequently lowering intestinal calcium absorption [13] and increasing urinary calcium excretion [14]. Inhibition of osteoblast (OB) activity and enhanced apoptosis of OB and osteocytes have been also observed [12, 15]. An increase in the levels of receptor activator of NF-κB ligand (RANKL) and a reduction in osteoprotegerin levels (OPG) have also been reported [16]. Finally, GCs depress the hypothalamic pituitary gonad axis, leading to a reduction in the production of estrogen [17], testosterone [18] and adrenal androgens [19], which are involved in bone maintenance. The great number of these factors acting more or less alone or synergistically on various targets might help to explain why the severity of GC complications may differ greatly among individuals exposed to a similar GC dose, some patients being nearly completely spared and other suffering from a host of fractures.

Diagnostic approach for therapeutic strategy

The operational diagnosis of postmenopausal OP has been based on BMD measurements by dual energy X ray absorptiometry (DXA) [20]. A T-score less than –2.5 has been used as a threshold for indicating pharmacological therapy. However, in GC therapy, some

convergent data tend to demonstrate that fractures might occur at a BMD level above the more conventional value of –2.5 usually applied in postmenopausal osteoporosis [5, 6, 7], leading to the proposal of using a T-score of –1 to –1.5 as the threshold for preventative therapy in GC-treated patients [21, 22, 23].

When to start therapy?

As bone loss and the incidence of fracture increase rapidly after the initiation of GC therapy, an optimal therapeutic intervention should be implemented as soon as GCs are started, evidently only if the duration of GC therapy is to last longer than 3 months. There is indeed some evidence that bone loss can be reversible when GC therapy is stopped after a short period of time [24]. Primary prevention should be aimed at preventing the rapid bone loss induced by GCs shortly after the initiation of GCs (e.g., starting not later than after 3 months of GCs), having in mind the hope of decreasing the fracture risk. In patients who have already been on GCs for a longer period of time, who have already experienced bone loss (and maybe fractures), secondary prevention or therapy could also start. In GC-OP, the sentence "it is never too early and never too late to treat" should apply [23].

Preventative and therapeutic approaches

General measures

Non-pharmacological prevention of fractures should be considered for GC-OP, as for other causes of OP [25]. In particular, the patients on GC should have a diet rich in calcium and protein. Weight-bearing exercise is highly recommended if the underlying condition allows their performance in order to maintain muscle mass, which could be potentially endangered by GC therapy [26]. However, there is no hard evidence about their role, their intensity or their time schedule. According to the condition necessitating their use, GCs should be prescribed at the lowest dose and for the shortest duration possible to minimize aftereffects, as the fracture risk increases with increasing daily doses [1], cumulative doses and treatment duration [4, 5, 6, 27]. Alternate day therapy does not impair too much growth in children, but does not really reduce BMD loss in adults [28, 29], possibly because of the persistent depression of adrenal androgen secretion [30]. Inhaled steroids, more and more frequently used in chronic obstructive pulmonary diseases, if less aggressive than oral GCs, are probably not completely devoid of skeletal complications [31, 32]. Intravenous pulses of high-dose methylprednisolone (up to 1 g) do not seem to be too detrimental to bone [33]. Repetitive administration could, however, be deleterious for bone quality.

Nonetheless, a rapid and complete weaning from GCs is rarely to be envisioned, and if the skeleton is less endangered by daily doses $\leq$ 5–7.5 mg equivalent prednisolone, it should be remembered that there is no really safe dose. This justifies the monitoring of BMD also in patients on low-dose GC, even if pharmacological preventative therapy is less mandatory.

Several bone-seeking agents aimed at preventing and/or reversing bone loss have been studied in randomized trials. They comprise calcium, vitamin D and its metabolites, hormone replacement therapy (HRT), bisphosphonates, fluoride salts and parathyroid hormone (PTH) [34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97].

Calcium and vitamin D

Calcium alone

As intestinal calcium absorption is impaired by GC therapy, its seems logical to increase calcium intake in the diet or by supplementation. However, in most studies in which calcium served as the control therapy, bone loss was not completely stopped by isolated calcium supplementation [34, 35, 50, 54, 78, 89], suggesting that calcium alone is not sufficient to prevent rapid bone loss in patients starting high-dose glucocorticoids [96]. Whether simple calcium supplementation can decrease bone loss in chronic GC users has not been convincingly demonstrated so far. No study addressing the use of calcium alone in GC-OP for fracture prevention is available.

Calcium and vitamin D

In a meta-analysis, both cholecalciferol (from 300 IU per day to 100,000 IU per week) plus calcium, activated vitamin D metabolites or analogs such as dihydrotachisterol were more efficacious in preserving BMD than either no therapy at all or calcium alone [36, 37]. However, the trials reviewed did not possess the power to determine which vitamin D formulation was more effective for fracture prevention [36, 37]. Plain cholecalciferol [38, 39, 40, 41, 42, 43], dihydrotachysterol (0.1 mg every other day) [44], calcidiol (35–40 μg/day) [45, 46, 47, 48], calcitriol (0.5–1.0 μg/day) [49, 50, 51, 52] and alfacalcidol (0.5–1.0 μg/day [53, 54, 55] seem to preserve BMD equally [36]. In a small controlled study in patients on long-term GC therapy, however, alfacalcidol (1 μg + 500 mg calcium per day; $n = 42$) had a larger effect than plain cholecalciferol (1,000 IU + 500 mg/day; $n = 43$) on mean lumbar BMD, but only a positive trend on vertebral fractures [55]. At the end of the 3-year study, 12 new vertebral

fractures had occurred in 10 patients of group 1α and 21 in 17 patients of group D3 (difference = NS). The occurrence of nonvertebral fractures was not different between groups. No effect was evident on femoral neck BMD [55]. In another larger study ($n = 145$) performed in patients just starting GCs, after 1 year alfacalcidol (1 μg + 405 mg calcium/day) produced a small increase in lumbar BMD (+0.39%) versus a loss of 5.7% in the placebo group (+ calcium), the difference between the two groups being significant ($P = 0.02$) [54]. There was no fracture assessment in this study [54]. Calcitriol [(0.5–1.0 μg + 1,000 mg calcium in association or not with salmon calcitonin (sCT) nasal spray (400 IU/day)] was compared with calcium alone in patients starting long-term GC therapy [50]. Therapy lasted 1 year. Calcitriol (mean dose 0.6 μg/day), with or without sCT, prevented more bone loss from the lumbar spine (mean rates of change –0.2 and –1.3 percent per year, respectively) than calcium alone (−4.3% per year, $P = 0.0035$). Bone loss at the femoral neck was not significantly affected by any treatment. In the second year, lumbar bone loss did not occur in the group previously treated with sCT plus calcitriol (+0.7% per year); it did still occur both in the group given calcium alone (−2.3% per year) and in the group given calcitriol alone (−3.6%), but the latter group received more GC in the 2nd year than the other two groups. Bone was lost in the femoral neck in all groups during the 2nd year, but there were no significant differences between the groups [50]. In another study in patients within 4 weeks of undergoing cardiac or single lung transplantation, calcitriol (0.50–0.75 μg + calcium 500 mg/day) was compared to a placebo (+ calcium). Treatment with calcitriol for 12 months followed by calcium for 12 months resulted in similar proximal femoral bone loss to that seen in those patients treated with calcium for 24 months. Bone loss at the proximal femur was significantly reduced or prevented by treatment with calcitriol for 2 years compared with treatment with calcium alone [51]. This suggests calcitriol prophylaxis needs to be continued beyond 12 months. At the lumbar spine, there were no significant differences in BMD between groups. The sample size was too low to provide reliable interpretation of vertebral fracture rates [51]. Therefore, the existing data are in favor of a preventative action of active metabolites of vitamin D as far as BMD is concerned. No consistent data exist, also not for an assessment of the fracture rate. It should be recalled, however, that the risk of developing hypercalcemia and hypercalciuria is greater with the activated vitamin D metabolites than with plain cholecalciferol. Taking that into account, supplemental calcium plus vitamin D3 should be considered as an adjunct therapy for more potent drugs, and their use as isolated therapy reserved for patients on low dose GCs (less than 7.5 mg/day equivalent prednisolone) or in the first 3 months of therapy, if weaning from GC can be considered.

Hormone replacement therapy

As GC use is associated with hypogonadism, hormone replacement therapy (HRT) could be envisaged in early postmenopausal women or in men without any contraindication. There is, however, no trial large enough to assess the role of HRT in fracture prevention in either women or men [56, 57, 58]. It is unlikely, however, that HRT will be used routinely in long-term GC-OP prevention, just like for postmenopausal OP prevention [59].

In men, testosterone replacement therapy has been shown to counteract bone and muscle mass loss resulting from GC therapy in a study of 1-year duration [58]. In this study, nandrolone decanoate had a positive effect on muscle mass, but not on BMD [58]. No primary prevention trial has been published yet. In any case, HRT in men should only be considered if low androgen levels are evidenced.

Calcitonin

CT as parenteral injections and intranasal spray has been shown to counteract bone loss in GC therapy, at least at the spine, both in primary prevention and in therapy trials [50, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71]. No efficacy on femoral neck bone loss, on vertebral and/or nonvertebral fractures was evidenced in a recent Cochrane review on 221 patients randomized to CT and 220 to placebo [71]. It should be recalled that only spinal BMD changes have to be considered for the primary endpoint in trials of primary prevention of GC-induced bone loss, according to the GREES recommendations [21].

Bisphosphonates

Disodium etidronate

Cyclic etidronate (400 mg/day for 14 days, followed by calcium 500 mg/day without vitamin D supplementation) increased the lumbar BMD significantly both in primary and secondary prevention studies. The effect on femoral neck BMD was less impressive [67, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84]. Only four studies have reported a vertebral fracture rate with etidronate therapy, three in primary prevention [77, 78, 82] and one in secondary prevention (more than 9 months on GC therapy) [39]. No significant difference in the vertebral fracture rate was observed between the etidronate-treated and placebo groups [39, 77, 82]. A significant reduction in the proportion of postmenopausal women with new vertebral fractures was observed in one study in the etidronate group as compared with the placebo group (respectively, 1 of 31 patients versus 7 of 32

patients; $P = 0.05$) [78]. In another study, more symptomatic fractures occurred in the etidronate group than in the control group (4 versus 0) [77]. However, these studies were not tailored to demonstrate antifracture efficacy.

Pamidronate disodium

In patients requiring first-time, long-term GC therapy at a daily dose of at least 10 mg of prednisolone, intravenous pamidronate administered as a single 90-mg infusion or on a 3-month regimen (a beginning intravenous dose of 90 mg followed by 30-mg infusions every 3 months) has been shown to effectively achieve primary prevention of GC-OP over 1 year as far as lumbar spine and hip BMDs are concerned [35].

Alendronate sodium

Oral alendronate (ALN) 2.5 mg, 5 or 10 mg + 800 to 1,000 mg of elemental calcium and 250 to 500 IU of vitamin D daily were tested versus a placebo plus the same supplementation for 48 weeks in patients on GC for less than 4 months, 4 to 12 months or more than 12 months (Table 1) [85]. Lumbar BMD increased significantly as compared to base line values and to placebo values in the 5 and 10 mg ALN groups (+2.1% and +2.9%, respectively) and non-significantly in the 2.5 mg ALN group (+0.7%) versus a non-significant loss in the placebo group (−0.4%). The bone loss was more marked, although not significantly, in the less than 4 months group. At the femoral neck, BMD decreased significantly—1.2% ($P < 0.01$) in the placebo group—but increased significantly versus the placebo and base line values in the 5 (+1.2%) and 10 mg (+1.0%) ALN groups. There was no significant difference in the vertebral fracture rate between the placebo group and the combined 5 and 10 mg ALN groups. In a post-hoc analysis, a borderline significance was observed between the incidence of vertebral fractures in postmenopausal women in the 5–10-mg ALN groups and the placebo group. The incidence of nonvertebral fractures was identical in the ALN and the placebo groups (4.4%) [85]. In the 1-year extension study, the 2.5-mg ALN dose was blindly switched to a 10-mg dose, the 5- and 10-mg doses and calcium and vitamin D supplementation remaining unchanged [86]. The mean lumbar spine BMD increased by 2.8, 3.9 and 3.7%, respectively, in the groups that received 5 mg, 10 mg and 2.5/10 mg of ALN daily ($P < 0.05$ versus placebo) and decreased by −0.8% in the placebo group (P = NS) over 24 months. BMD was maintained at the femoral neck in patients receiving any dose of ALN. There were fewer patients with new vertebral fractures in the ALN group versus the placebo group (0.7 versus 6.8%; $P = 0.026$). The safety profile was similar between treatment groups [86]. In another study of ALN versus calcitriol for the primary prevention of bone loss after cardiac transplantation, after 1 year, the BMD at the lumbar spine had decreased by a mean of −0.7% in the ALN group (10 mg/day) and −1.6% in the calcitriol group (0.5 μg/day) versus −3.2% in the reference untreated group [87]. At the femoral neck, the BMD decreased by a mean of −1.7% in the ALN group, −2.1% in the calcitriol group and −6.2% in the reference group. The incidence of vertebral fractures did not differ significantly among the groups (6.8% in the ALN, 3.6% in the calcitriol and 13.6% in the reference group). Hypercalciuria developed in 27% of the patients in the calcitriol group and 7% of those in the ALN group ($P = 0.01$) [87]. The necessity to monitor serum and urine calcium during calcitriol therapy plays in favor of the use of ALN.

Risedronate sodium

In a preliminary study, 120 postmenopausal women with rheumatoid arthritis who required long-term (>6 months) treatment with oral GCs at an average daily dose of at least 2.5 mg prednisolone received either a placebo, 2.5 mg risedronate (RIS) daily or cyclical 15 mg RIS (15 mg RIS for 2 weeks followed by a placebo daily for 10 weeks) [88]. The patients received the study drug for 96 weeks (nearly 2 years; eight cycles for patients on cyclical RIS), then underwent a 48-week non-treatment follow-up for a total of 144 weeks (3 years). The overall RIS dose was the same for both active treatment groups [88]. Contrary to all other studies dealing with GC-OP, this study was restricted to patients with the same condition, i.e., rheumatoid arthritis. At 97 weeks, the BMD was maintained at the lumbar spine (+1.4%) and femoral neck (−1.0%) in the daily 2.5 mg RIS group, while there was significant bone loss at these skeletal sites in the placebo group (−1.6% and −3.6%, respectively). The difference between the two treatment groups was not significant. During the non-treatment follow-up period, the mean change from base line in BMD at the lumbar spine was −0.1% in the placebo group, −1.2% in the daily 2.5 mg RIS group ($P < 0.03$) and −2.3% in the cyclical 15 mg RIS group ($P < 0.002$). The changes at the femoral neck were −0.3% in the placebo group, −1.2% in the daily 2.5 mg RIS group and −0.8% in the cyclical 15 mg RIS group. There was no statistically significant difference within or between groups at the femoral neck during the follow-up period. Incident vertebral fractures at 2 years were found in 3 of 33 patients in the placebo group, 7 of 31 in the daily 2.5 mg RIS group and 2 of 30 in the cyclical 15 mg RIS group [88].

The results of two studies on GC-OP, one corresponding to a first prevention study [89] and the second to a treatment study [90], were pooled together in a third report [91] in order to reach statistical power for the fracture incidence study (Table 1). However, it should be recalled that the analysis of the pooled study data was not prospectively planned. Men and women ($n = 518$)

Table 1 Percentage changes in bone mineral density, vertebral and non-vertebral fractures in alendronate and risedronate

Controlled trials

Study	Total *n* At start (Medical condition)	Population Gender (Age range) Initial GC dosage	GC duration Months	Follow-up Duration Months	Treatment groups	% Change LS BMD	% Change F. neck BMD	% Change Trochanter BMD	Vertebral Fractures %	Non-vertebral Fractures %
K.G. Saag	477	M; F	< 4 (34%)	(48 weeks)	Ca 800–1,000 mg + Vit D 250–500 IU	−0.4	−1.2[†]	−0.7	3.7	4.4
[85]	(A)	(17–83)	4–12 (21%)		ALN 2.5 mg + Ca 800–1,000 mg + Vit D 250–500 IU	0.7	NA	NA	NA	NA
1998		> 7.5 mg	> 12 (45%)		ALN 5 mg + Ca 800–1,000 mg + Vit D 250–500 IU	2.1[‡]	1.2[†]	1.1[†]	2.3[$]	4.4[$]
					ALN 10 mg + Ca 800–1,000 mg + Vit D 250–500 IU	2.9[‡]	1.0[†]	2.7[‡]	2.3[$]	4.4[$]
J.D. Adachi	208	M; F	< 4 (32%)	24	Placebo + Ca 800–1,000 mg + Vit D 250–500 IU	−0.77	−2.93	−1.21	6.8	9.8
[86]	(A)	(17–83)	4–12 (21%)		ALN 5 mg + Ca 800–1,000 mg + Vit D 250–500 IU	2.84[§§]	0.11[§§]	2.16[§§]	0.7[$§]	5.4[$]
2001		> 7.5 mg	> 12 (47%)		ALN 10 mg + Ca 800–1,000 mg + Vit D 250–500 IU	3.85[§§]	0.61[§§]	3.91[§§]	0.7[$§]	5.4[$]
					ALN 2.5 mg/10 mg + Ca 800–1,000 mg + Vit D 250–500 IU	3.69[§§]	−0.43[§§]	1.73[§§]	0.7[$§]	5.4[$]
E. Shane	149	M; F	1	12	Ca 945 mg + Vit D 1,000 IU	−3.2	−6.2	NA	13.6	NA
[87]	(B)	(18–70)			ALN 10 mg + Ca 945 mg+	−0.7[§]	−1.7[##]	NA	6.8	NA
2004		50 mg			Calcitriol 0.25 μg + Ca 945 mg + Vit D 1,000 IU	−1.6	−2.1[##]	NA	3.6	NA
R. Eastell	120	F	> 6	(97 weeks)	Placebo	−1.6°	−3.6[†]	−4.0[†]	9	NA
[88]	(C)	(PM)			Ris 2.5 mg	1.4*	−1.0	−0.4[§]	22.6	NA
2000		> 2.5 mg			Ris 15 mg/ day (cyclical regimen: 2 out of 12 weeks)	−0.05	0.9	1.3*	6.6	NA
S. Cohen	224	M; F	< 3	12	Placebo + Ca 500 mg	−2.8	−3.1	−3.1	17.3	5.2
[89]	(A)	(18–85)			Ris 2.5 mg + Ca 500 mg	−0.1	−0.4	−0.2	11.1	4
1999		> 7.5 mg			Ris 5 mg + Ca 500 mg	0.6[#]	0.8[#]	1.4[#]	5.7	3.9
D.M. Reid	290	M; F	> 6	12	Placebo + Ca 1,000 mg + Vit D 400 IU	0.4	−0.3	1.0	15	6
[90]	(A)	(18–85)			Ris 2.5 mg + Ca 1,000 mg + Vit D 400 IU	1.9[‡]	−0.2	0.1	5[$§]	9

Table 1 (Contd.)

Controlled trials

Study	Total *n* At start (Medical condition)	Population Gender (Age range) Initial GC dosage	GC duration Months	Follow-up Duration Months	Treatment groups	% Change LS BMD	% Change F. neck BMD	% Change Trochanter BMD	Vertebral Fractures %	Non-vertebral Fractures %
2000		>7.5 mg			Ris 5 mg + Ca 1,000 mg + Vit D 400 IU	2.9‡	1.8‡	2.4‡	5§§	8
S. Wallach	518	M; F	2 groups	12	Placebo + Ca 500–1,000 mg + Vit D 400 IU	−1.0	−1.5	−0.8	16	6
[91]	228 (N Am)	(18–85)	< 3 (N Am)		Ris 2.5 mg + Ca 500–1,000 mg + Vit D 400 IU	1.3	−0.3	−0.01	7	7
2000	290 (Eur)	>7.5 mg	>6 (Eur)		Ris 5 mg + Ca 500–1,000 mg + Vit D 400 IU	1.9$^{\#}$	1.3$^{\#}$	2.0$^{\#}$	5*	6
D.M. Reid	184	M	<3	12	Placebo + Ca 500 mg	−3.4†	−3.3†	−3.4†	24	NA
[92]	P 77	(18–85)			Ris 2.5 mg + Ca 500 mg	NA	NA	NA	0$^{*\$\$}$	NA
2001		>7.5 mg			Ris 5 mg + Ca 500 mg	NA	NA	NA	9$^{*\$\$}$	NA
D.M. Reid	184	M	>6	12	Placebo + Ca 1,000 mg + Vit D 400 IU	NA	NA	NA	NA	NA
[92]	T 107	(18–85)			Ris 2.5 + Ca 1,000 mg + Vit D 400 IU	NA	NA	NA	NA	NA
2001		>7.5 mg			Ris 5 mg + Ca 1,000 mg + Vit D 400 IU	4.8†	2.1†	2.6†	NA	NA

$^{\S}P < 0.05$ vs. placebo; $^{\S\S}P \leq 0.05$ vs. placebo; $^{*}P < 0.01$ vs. placebo; $^{\#}P < 0.001$ vs. placebo; $^{\#\#}P = 0.001$ vs. placebo; $^{\circ}P < 0.05$ vs. baseline; $^{\dagger}P < 0.01$ vs. baseline; $^{\ddagger}P < 0.001$ vs. baseline
$^{\$}$when active treatment groups were combined; $^{\$\$}$when data from two studies were combined in the pooled risedronate groups. A = various medical conditions; B = cardiac transplantation; C = rheumatoid arthritis; M = male; F = female; PM = post-menopausal; P = prevention; T = treatment

receiving moderate-to-high doses of GCs were enrolled in two studies with similar protocols and randomly assigned to receive either a placebo or RIS (2.5 or 5 mg) for 1 year. All patients received daily calcium supplementation (500–1,000 mg), and most also received supplemental vitamin D (400 IU). In the overall population, the mean lumbar spine BMD increased +1.9% from base line in the RIS 5 mg group ($P < 0.001$) and decreased −1.0% in the placebo group ($P < 0.01$) after 1 year. BMD at the femoral neck increased +1.3% in the 5 mg RIS group versus a loss of −1.5% in the placebo group. The RIS 2.5 mg dose was less efficacious than the 5-mg dose, with a significant increase from baseline in lumbar spine BMD at 12 months (+1.3%), and no significant change from baseline at the femoral neck. Patients receiving risedronate 5 mg and RIS 2.5 mg had a 70% and a 58% reduction in vertebral fracture risk, respectively, compared with the placebo group ($P = 0.01$ and $P = 0.08$) [91]. Only a trend towards a reduction in the incidence of vertebral fractures was observed in each of the individual studies [89, 90], but in the treatment study, combining the 2.5- and 5-mg RIS treatment groups allowed to achieve significance in the reduction of the fracture rate ($P = 0.042$) [90]. The positive effect of 5 mg RIS in the reduction of the fracture rate was evident across the various conditions necessitating GC therapy [92]. A treatment effect (5-mg RIS versus placebo) was also seen in patients both with and without prevalent vertebral fractures at baseline. Fewer patients in the RIS groups experienced multiple vertebral fractures compared with the placebo group. Non-vertebral fractures were observed with a similar incidence among groups [91]. The analysis of the subgroup of men from the two above-mentioned studies [89, 90] demonstrated a decrease of 82.4% of the incidence of vertebral fractures in the pooled RIS groups compared with the placebo group ($P = 0.008$) [92].

In their Cochrane review on bisphosphonates for steroid-induced osteoporosis, Homik et al. concluded that BPs appear to be efficacious in preventing and treating corticosteroid-induced bone mineral loss at the lumbar spine [93]. There is a statistically significant treatment effect of BPs on femoral BMD, although the magnitude is smaller than that seen at the lumbar spine [93]. As most of the studies were of short duration, they stated that at this time, the long-term effects regarding efficacy beyond 1 year or efficacy against spinal fractures cannot be adequately established, except by extrapolation [93]. They concluded that despite these cautions, BPs remain a promising therapy for preventing the significant osteoporosis associated with GC use. The data suggest that primary prevention is more efficacious than secondary prevention [93].

In our opinion, the data pertaining to fracture prevention in GC-OP, even if some pooling of the data is needed to reach statistical power, seem to be stronger for alendronate and risedronate than for etidronate. Other bisphosphonates such as intravenous zoledronic acid are currently under study in GC-OP.

Promotors of bone formation

Considering that in GC-OP, bone formation is severely depleted [12, 15], it seems to be logical to look for the use of promoters of bone formation in order to stimulate it.

Fluoride salts

In a recent meta-analysis, fluoride efficacy was estimated to be intermediate between bisphosphonates and vitamin D or calcitonin, but only small numbers of studies are involved in the therapy of GC-OP with fluoride and do not allow greaater conclusiveness [37]. In particular, no study has assessed the anti-fracture efficacy of fluoride salts.

Parathyroid hormone

This report does not include a full discussion on parathyroid hormone because of the scarcity of the trials in GC-OP [94, 95]. Teriparatide [recombinant human parathyroid hormone (1–34)] is currently under study in the treatment of GC-OP.

Conclusion

The prevention and treatment of GC-OP should be considered in postmenopausal females and osteopenic premenopausal females and males put on a daily dose of at least 7.5 mg equivalent predniso(lo)ne that is expected to be maintained at least 3 months. Non-pharmacological interventions (e.g., exercise, tobacco and alcohol cessation) have not been shown to be associated with a reduction in fracture risk in GC-OP. However, they should obviously be recommended not only for bone protection, but also for the prevention of muscle atrophy induced by GC.

Supplemental calcium and vitamin D should be considered as a first-line therapy in the management of GC-OP. Owing to the decrease in intestinal calcium absorption provoked by GCs and the rather low dietary intake of calcium in the Belgian population, systematic supplementation of 500–1,000 mg elemental calcium should be highly recommended in patients starting GC therapy and/or already on GC therapy for months. Likewise, the prevalence of vitamin D deficiency in patients (ambulatory or not) would justify the supplementation of cholecalciferol (at least 800 to 1,000 IU/day). Active metabolites of vitamin D3 may be more potent for BMD maintenance than calcium alone and/or calcium plus plain vitamin D, but there is no definitive evidence that active metabolites of vitamin D could be more effective in reducing fracture risk than plain vitamin D and calcium. Therapy with calcium and vitamin D supplementation alone should be reserved for patients taking less than 5–7.5 mg equivalent prednisolone daily whose BMD results are still within the normal range.

They should also be prescribed to patients for whom GC therapy is expected to last less than 3 months. In other situations, calcium plus vitamin D should be considered as an adjuvant therapy to other more potent drugs.

HRT could be considered in young postmenopausal women on GC. The same considerations as those proposed in postmenopausal OP should prevail [25]. In GC-OP men, the use of testosterone replacement has been advocated [58]. However, no fracture data exist for such therapies. In any case, testosterone should be considered only in men with low androgen levels. Their potential after-effects should preclude long-term use. No study on SERMs has been published so far in GC-OP, except for a small and promising study with tamoxifen [97].

CT appears to possess a predominant effect on trabecular bone in GC-OP just as in PM-OP. The effect on the hip BMD is less certain. If CT is able to maintain lumbar BMD, its antifracture efficacy remains to be demonstrated. There is an increasing body of evidence supporting antifracture efficacy for BPs with ALN and RIS, especially when pooling several studies together and when taking into account the positive results obtained with both drugs in large trials in PM-OP [21]. The data on etidronate are much less convincing as far as anti-fracture efficacy is concerned. Furthermore, the availability of ALN and RIS has rendered obsolete the use of etidronate in GC-OP, just as has been the case for PM-OP.

As far as the duration of (preventative or curative) therapy of GC-OP is concerned, treatment with bisphosphonate should be maintained as long as the patient is on GC therapy at a dose equal or superior to 7.5 mg equivalent prednisolone daily [98]. There is no rationale to prolong therapy after the patient has been weaned from GC (or even takes a very low dose), because there is evidence of some recovery of the skeleton when GCs can be stopped [24]. An exception could be patients with established postmenopausal OP, who should be treated according to their OP status.

Just like in PM-OP, there is currently no room in GC-OP for any combination therapy of two antiresorptive agents (calcium and vitamin D excepted) and/or of an antiresorptive and an anabolic agent. There is no proof that the increased costs induced by the concomitant administration of two agents will be translated into an increased therapeutic efficacy.

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