EXPERT OPINION

1. Introduction
2. Epidemiology
3. Pathophysiology
4. Management options
5. GIOP management
6. Expert opinion

Management of glucocorticoid-induced osteoporosis: clinical data in relation to disease demographics, bone mineral density and fracture risk

Eustathios Kenanidis, Michael E Potoupnis, Panagiotis Kakoulidis, Andreas Leonidou, Grigorios T Sakellariou, Fares E Sayegh & Eleftherios Tsiridis†

Aristotle University Medical School, Academic Orthopaedic Unit, Thessaloniki, Greece

Introduction: Glucocorticoid-induced osteoporosis (GIOP) is the most common type of secondary osteoporosis. Patient selection and the treatment choice remain to be controversial. None of the proposed management guidelines are widely accepted. We evaluate the available clinical data, the efficacy of current medication and we propose an overall algorithm for managing GIOP.
Areas covered: This article provides a critical review of *in vivo* and clinical evidence regarding GIOP and developing evidence-based algorithm of treatment. Data base used includes MEDLINE® (1950 to May 2014).
Expert opinion: Patient-specific treatment is the gold standard of care. Glucocorticoid (GC)-treated patients must comply with a healthy lifestyle and receive 1000 mg of calcium and at least 800 mg of Vitamin D daily. Bisphosphonate (BP) therapy is the current standard of care for prevention and treatment of GIOP. Most of bisphosphonates demonstrated benefit in lumbar bone mineral density (BMD) and some in hip BMD. Alendronate, risedronate and zoledronate showed vertebral anti-fracture efficacy in postmenopausal women and men. Scarce data however when compared head to head with BP efficacy. In post-menopausal women, early antiresorptive BP treatment appears to be efficient and safe. In premenopausal women and patients at high risk of fracture receiving long-term GC therapy however, teriparitide may be advised alternatively.

Keywords: glucocorticoid, glucocorticoid-induced osteoporosis, management, osteoporosis

Expert Opin. Drug Saf. [Early Online]

1. Introduction

Glucocorticoids (GC) are among the most commonly prescribed drugs due to their unsurpassed anti-inflammatory and immunomodulatory actions [1]. They are used in the management of various rheumatological, dermatological, respiratory and other medical conditions. However their long-term use causes several side effects.

The most crippling complication of GC therapy consists of secondary osteoporosis [2]. GC remain the leading cause of iatrogenic osteoporosis and one of the most common types of osteoporosis overall. Its epidemiology, pathophysiology and treatment guidelines differ substantially compared with postmenopausal osteoporosis (PMO).

informa
healthcare

10.1517/14740338.2015.1040387 © 2015 Informa UK, Ltd. ISSN 1474-0338, e-ISSN 1744-764X

Article highlights.

- Indication for GIOP treatment: daily dose of at least 7.5 mg prednisolone (or equivalent) for 3 months in postmenopausal or osteopenic premenopausal women and men.
- Ca/vit D is adjuvant therapy in GIOP management and their intake should exceed the corresponding intake in POM: at least 500 – 1000 mg Ca and 800 mg vit D per os daily is recommended.
- Bisphosphonate (BP) therapy is the current standard of care for prevention and treatment of GIOP.
- Most of BP demonstrate beneficial effect in lumbar BMD; several BP showed efficacy in increasing hip BMD and vertebral fracture risk reduction.
- Teriparatide could be considered the first choice for the treatment of GL-treated patients who are at high risk of fracture, those with low BMD and for those receiving long-term GL therapy as well as in premenopausal women.

This box summarizes key points contained in the article.

This article reviews the currently available literature on existing treatment regimens in GC-treated patients.

2. Epidemiology

More than 1% of adults are treated with GC annually [3,4]. In 2000, 0.9% of the total adult population from General Practice Research Database in the United Kingdom used oral GC (2.5 – 7.5 mg prednisolone or equivalent) at any one time [5].

Both daily and cumulative GC doses as well as treatment duration affect the incidence of the glucocorticoid-induced osteoporosis (GIOP) [6]. Doses > 7.5 mg revealed fivefold risk of vertebral and twice risk of hip fractures [6].

GIOP is associated with rapid bone loss and increased fracture risk especially within the first 3 – 6 months of oral GC therapy initiation, followed by slowing in subsequent years [7,8]. A fracture may be the first occurrence of the disease and ~ 30% of patients treated will suffer from a fracture during treatment [3,4,9].

Past and current GC treatment accounts for an increased fracture risk unrelated to the bone mineral density (BMD) [9]. The underlying disease itself the age, the menopausal status, fracture history and other demographic characteristics often contribute to bone loss [10,11].

GIOP is a distinct medical condition that needs to be considered at the time of GC initiation in all patients, even in those carrying the lowest risk of osteoporosis [12]. Physician's familiarity with GIOP has improved but remains less than ideal especially in young patients, men and those not treated by specialists [13]. Treatment compliance for GIOP ranges between 40 and 50% [14,15]. A main challenge is the improvement of physician and patient's awareness of the risks associated with GIOP.

3. Pathophysiology

The pathophysiology of GIOP is particularly complex. The effects of GC on bone cells and mineral metabolism are dose and time dependent [1,16]. Although at physiological concentrations GC are outstanding regulators of mesenchymal cell differentiation and function, at supraphysiological concentrations GC may have deleterious effects on them [1]. These effects are mediated via genomic and non-genomic actions [17] and evoke bone changes at a microarchitectural level. The most important mechanism of GC involves translocation of the complex of GC and the GC cytosolic receptor into the nucleus causing changes in gene expression [17]. BMD measurement, however, frequently is unable to detect these initial bone quality changes [16,18].

The pathogenesis of GIOP is fundamentally different compared to PMO [19]. The detrimental effect of GC on bone is mainly due to a reduction in bone formation whereas the number of osteoclasts remains almost unaffected [12,20,21]. GC affect osteoblasts, osteocytes and osteoclasts via direct and indirect mechanisms [1].

3.1 Direct effects of GC on bone metabolism

Cardinal mechanisms of GC action comprise the increased apoptosis of mature osteoblasts and osteocytes, impaired differentiation of osteoblasts, and an elongation of osteoclasts' lifespan [8,22].

3.1.1 Osteoblasts

GC reduce the number and unsettle the function of osteoblasts mainly through impairment of osteoblastogenesis and osteoblastic differentiation and maturation [8,21].

The Wnt/β-catenin signaling pathway is crucial for the differentiation of mesenchymal stem cells toward mature osteoblasts [23]. This pathway is activated by the binding of a Wnt-protein ligand to the low-density lipoprotein receptor-related proteins 5 and 6 and its co-receptor, frizzled that stabilizes b-catenin, which regulates gene transcription and subsequently induces bone formation [24,25]. Dickkopf-1 (Dkk-1) and sclerostin (mostly synthesized by osteocytes) are Wnt pathway inhibitors [26,27]. GC enhances Dkk-1 and sclerostin expression thus inhibiting bone formation [26-31].

In addition GC appears to be responsible for the redirection of bone marrow stromal cells differentiation toward adipocytes instead of osteoblasts [32-36]. This preferential shift of stromal cells towards adipodytes is mediated by an upregulation of the peroxisome proliferator-activated receptor-g2 (PPARγ 2) and suppression of both the osteogenic transcription factor runt-related protein 2(Runx2) and the activator protein 1 [29,36,37]. Continuous GC treatment stimulated adipocyte differentiation, but failed to induce Osterix expression and mineralized matrix formation [32].

Finally GC may also provoke apoptosis of osteoblasts and osteocytes [22] through activation of caspase 3 [38].

Yun *et al.* specifically demonstrated that apoptosis of osteoblasts is related to the activation of glycogen synthase kinase 3b, a specific protein kinase implicated in the Wnt/catenin pathway [29,39].

3.1.2 *Osteocytes*

Osteocytes have also a central role in the pathogenesis of GIOP. GC induce the apoptosis of osteocytes due to the activation of caspase 3 [23,38] or via specific intracellular kinases, the related focal adhesion tyrosine kinase and c-Jun N-terminal kinase [40,41]. In addition even direct osteocyte autophagy could be induced by specific GC like dexamethasone [42].

The anticipated reduction of osteocytes impede the osteocyte-canalicular network communication [8] thus resulting in failure of expressing the signals responsible for bone regeneration [38,43,44]. It has been suggested that osteocyte-canalicular interruption alone could induce apoptosis of the surrounding osteocytes, compromising the mechanical properties of the bone [44,45].

3.1.3 *Osteoclasts*

Excess of GC reduce apoptosis and increase lifespan of osteoclasts [8,46]. Macrophage colony stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANK-L) constitute the group of essential cytokines for the differentiation of osteoclasts [47]. GC augment the expression of M-CSF and RANK-L, in stromal and osteoblastic cells [23,48]. Osteoclast apoptosis is also suppressed during GC therapy, through inhibition of the osteoprotegerin (OPG) [19,49]. Following however, GC therapy the ensuing considerable reduction of osteoblastic cells diminishes the RANK-L production thus reducing the osteoclasts. Fracture risk induction at the early stages of GC treatment that is 'paradoxically' reduced later on during the treatment course may be explained by the latter sequence. Other possible mechanisms of the osteclastic induction are the enhancement of Interleukin-6 and the suppression of interferon-beta expression [50].

Additionally the effect of GC might also be connected with innocuous function of osteoclasts [22]. Kim *et al.* revealed that GC may have an adverse structural effect on osteoclasts ruffled border or disrupt the cytoskeleton thus resulting in indirect osteoclast 'de-activation' [51].

3.2 Indirect effect on bone metabolism

GC may also exert indirect effects on muscles, calcium metabolism and mineralization of bone mass. GC decelerate protein synthesis and accelerate protein breakdown [52] affecting muscle mass and strength. This so-called steroid myopathy enhances the risk of falls [53]. GC also affect calcium metabolism, which subsequently affects muscle function, by inducing hypocalcaemia caused either by reducing intestinal calcium absorption or increasing renal calcium clearance [8]. Finally uninterrupted exposure to GC has been shown to induce transrepression of two salient matrix proteins, osteocalcin and type 1 collagen that impair bone mineralization [29,54]. Overall, these effects on bone metabolism contribute to early and rapid bone loss and increased fracture risk [8].

4. Management options

GIOP management is not universally established via international consensus or globally acceptable guidelines. The evidence for the efficacy of interventions in GIOP is weaker compared to PMO. There is poor quality evidence regarding GIOP in premenopausal women, pediatric and older population.

Additionally the interpretation of existed data is also difficult. Early bone fragility following GC treatment is not directly correlated with changes in BMD measurement as in typical PMO [12]. It is very interesting that for the same BMD, patients who receive GC are at higher risk for fracture than patients not receiving GC [55]. Contrary to postmenopausal threshold for fracture risk currently at T-score of > 2.5, a lower T-score of -1 to -1.5 has been proposed as threshold for preventative treatment in glucocorticoid treated patients [9,56].

Furthermore the interpretation of the studies is even more difficult due to the small sample size usually used. Few studies were powered to detect differences in fracture incidence between treatments.

Complexity is also reinforced by the heterogeneity of the data involved in GIOP studies. A variety of pathologic conditions that need GC treatment are often associated with systemic bone loss and osteoporosis independently of the GC [1]. Heterogeneity concerns age, sex, concurrent treatments and whether a prevention or treatment type study is interpreted. Furthermore the deleterious effect of GC on bone metabolism can be largely modified by other factors such as individual GC sensitivity [57,58].

Fracture risk's prediction in patients on GC treatment is doubtful compared with PMO [1].The fracture risk of patients taking GC is related more with the diurnal dose and the period of GC therapy. It is well documented that a daily dose of 5 mg or more of prednisolone (or equivalent) for 3 months or greater is related with increased fracture risk [55,59]. Several national guidelines utilized this limit as a cutoff threshold for initiating anti-osteoporotic drugs [22,60-64]. Other guidelines have recommended however higher daily GC dose [2,65].

Recently the American College of Rheumatology [66] recommended guidelines for GIOP management based on patient's age, menopausal status, daily GC dose and fracture risk calculated with FRAX [67]. Treatment should be given to postmenopausal women and men ≥ 50 years at low risk for fracture (< 10%) when using GC ≥ 7.5 mg/day and at medium (10 – 20%) or at high risk for fracture (> 20%) when using any dose of GC. They also recommended startup of treatment to premenopausal women and men < 50 years with history of fragility fracture with no chance of pregnancy and use of GC for 1 – 3 months at doses ≥ 5 mg/day or

with chance of pregnancy and GC use ≥ 3 months at doses ≥ 7.5 mg/day.

Disadvantage of 2010 ACR guidelines is FRAX and DEXA availability [22,68]. FRAX was set by a panel of experts dichotomizing patients using GC for ≥3 months. More specifically GC users can enter FRAX when receiving GC for > 3 months on an average daily dose between 2.5 and 7.5 mg of prednisolone or its equivalents [69]. FRAX accommodates only hip but not spine BMD or vertebral fractures and does not include the daily GC dosages. Furthermore, ACR guidelines are not easily applicable in countries where DEXA is not widely available [59].

A working group of the International Osteoporosis Foundation (IOF) and European Calcified Tissue Society (ECTS) proposed in 2012 new treatment guidelines for GIOP, relegating the need of DXA but also inviting the development of independent national guidelines based on their recommendations [70]. Treatment is endorsed following fracture risk assessment but no standard intervention threshold was defined. Patients at high risk for fracture will start treatment without BMD testing whereas those at low risk will not initiate treatment and DXA will not be required. Patients belonging at the intermediate fracture risk group will start therapy depending on DEXA testing. Fracture risk assessment will be accomplished with the adapted FRAX tool to overcome some of its abovementioned limitations [69,71]. The re-evaluation of patients after treatment initiation is not also clearly defined. We usually repeat DEXA in these individuals once yearly.

There is limited evidence that bone loss may be reversible when GC treatment is discontinued after a short period of time [72]. Optimal intervention should be performed however immediately after GC initiation, especially if the duration of therapy is expected to exceed 3 months. Intervention implemented shortly after initiation of therapy (3 months) is usually referred as primary prevention whether treatment of patients that take GC for a longer period of time and bone loss have already occurred is mentioned as secondary prevention or treatment.

5. GIOP management

GIOP management involves non-pharmacological and pharmacological treatments. The efficacy of individual pharmaceutical agents in selected GIOP studies and where possible a brief description of the populations treated is presented.

5.1 Non-pharmacological treatment

5.1.1 General measures

Scarce evidence exists regarding general measures against GIOP. The majority of the recent treatment guidelines however include recommendations of lifestyle changes for the management of GIOP [1,66,70]. GC-treated patients should perform daily a balanced physical exercise to counteract bone loss and to avoid falling [73]. Falls appear to be more frequent in patients receiving GC due to steroid-induced myopathy [1]. Patients are also encouraged to cease smoking, restrict alcohol consumption to less than two standard drinks per day and follow a diet rich in protein and calcium [73]. As weight loss is associated with bone loss, patients should maintain normal body weight [12]. Steroid dose or type should be adjusted or minimized as needed and possible [59]. Alternate day therapy [74], intravenous (i.v.) corticosteroids [75] or GC sparing agents should be considered when possible.

5.1.2 Calcium and vitamin D

GC deregulate intestinal calcium absorption and renal calcium excretion [76,77]. Although oral replacement of the lost calcium seems to be reasonable, this has not been proved to prevent bone loss in patients starting high dose of GC or in long-term GC users [78-82]. The combination of calcium and vitamin D supplementation (cholicalciferol) or vitamin D analogs have been proven to be more effective compared to no therapy or calcium alone for the management of GIOP [82-93].

More specifically two meta-analyses [94,95] reported that calcium and vitamin D supplementation significantly prevent lumbar BMD loss compared to either calcium alone or no therapy in GC-treated patients. Amin *et al.* analyzing 21 studies showed also that vitamin D and calcium are less effective than Bisphosphonates (BP) and they had no fracture risk reduction in the management of GIOP [95]. Homik *et al.* analyzed five randomized trials including 274 patients that received calcium and vitamin D for 2 years [94]. He reported the beneficial effect in lumbar and forearm BMD compared with calcium alone or no therapy. However there was no benefit as far as femoral neck density, fracture risk and biochemical bone markers were concerned.

Calcium and vitamin D supplementation have been used as control therapy in randomized studies compared with certain antiosteoporotic drugs for prevention or treatment of GC-treated patients [80,96-99]. Although Calcium and vitamin D supplementation had a positive effect on lumbar BMD, they were much less effective than BP. It must be mentioned however that the efficacy of BP in GIOP has been demonstrated in these studies combined with calcium and vitamin D and not alone [96-99].

Solitary vitamin D or its analogs demonstrated also efficacy on the treatment of GIOP. Reginster *et al.* reported that the alfacacidol group demonstrated statistical significant greater change in lumbar BMD than the placebo group (6.06%, p = 0.02) in 145 GC-treated patients [100]. A meta-analysis of experimental studies revealed that supplements of active vitamin D derivatives (calcitriol, alfacalcidol and dihydrotachysterol) reduced lumbar bone loss (pooled effect size 0.35/ CI: 0.18, 0.52) and vertebral fracture risk (pooled effect size 0.56/ CI: 0.34, 0.92) more effectively than no treatment, placebo or calcium alone [101]. However vitamin D analogs were less effective than BP in BMD preservation and fracture risk reduction [101,102]. Other metanalyses reported that

vitamin D analogs had a greater beneficial effect in BMD and fracture risk than native vitamin D in postmenopausal women [83.84]. There is no enough evidence however to support that active metabolites of vitamin D as calcitriol or alfacacidol, either reduce fracture risk or they are more potent inhibitors of bone loss than native vitamin in GC-treated patients [83,84,95,103].

International guidelines (ACR/IOF) suggest daily supplementation with 1000 – 1500 mg of elemental calcium and 800 – 1000 IU of cholecalciferol in GC-treated patients [66,70]. Calcium consumption needs to be higher compared to PMO as a result of calcium balance deregulation induced by corticosteroids. Vitamin D supplementation should maintain adequate 25-hydroxyvitamin D3 serum level of at least 50 nmol/L during the whole year [104].

5.2 Pharmacological treatment

5.2.1 *Calcitonin*

Calcitonin (CALC) was mainly evaluated in randomized [105-107] or not placebo-controlled studies, with calcium and vitamin D supplements or no treatment in GC-treated patients [108-112]. It has been used both in prevention and treatment studies lasting from 6 months to 7 years [109].

Parenteral or intranasal (i.n.) administration of CALC appeared to be an effective treatment for the prevention of lumbar spine bone loss in GC-treated patients [82,105-112]. In a 7-year-trial, CALC was compared to placebo treatment in heart transplant recipients on maintenance immunosuppression [109]. During the first 3 years of treatment, CALC reduced significantly lumbar BMD compared to placebo ($p = 0.002$). There was no difference however between groups at 7 years ($p = 0.474$).

CALC had no effect in the prevention of femoral bone loss and reduction of vertebral and non-vertebral fractures [105-113]. In addition CALC showed inferior effectiveness compared to BP [107]. In a randomized controlled trial i.n. CALC administered at 200 IU/day compared with oral 10 mg/day alendronate (ALN) in GC-treated patients for two years [107]. Differences in lumbar and hip BMD between groups were significantly different favoring ALN group.

A Cochrane metaanalysis revealed that CALC was more effective than placebo at preserving lumbar spine bone mass after 6 and 12 months of therapy but not at 24 months in GC-treated patients [113]. CALC failed also to reduce significantly fracture risk compared to placebo both for vertebral (RR: 0.71, CI: 0.26 – 1.89) and non-vertebral fractures (RR: 0.52, CI: 0.14 – 1.96). CALC is no longer considered as GIOP therapy.

5.2.2 *Bisphosphonates*

BP are recommended as the first-line therapy for the prevention and treatment of GIOP by several international guidelines due to their anti-resorptive effectiveness [66,70]. BP reduce bone resorption and the rate of bone remodeling through various actions on osteoclasts; their effect on osteoblasts is limited [114]. The exact mechanism of BP's action however in GIOP has not been fully elucidated. Specific randomized controlled trials, demonstrated the efficacy of BP in the prevention and treatment of GIOP (**Table 1**) [80,96,115-119]. Most of them showed significant gain in lumbar BMD compared to placebo; several BP however demonstrated also efficacy in increasing hip BMD and fracture risk reduction (**Table 2**).

5.2.2.1 *Etidronate*

The efficacy of etidronate (ETN) in the treatment of GIOP has been evaluated in specific prospective cohort and controlled [80,120-128], or randomized controlled studies [115,129-132]. ETN was efficient in increasing lumbar BMD in both prevention [115,124,128,131] and treatment studies [80,120,122,123,129,130] even for a period of 7 years [133]. Few ETN studies demonstrated moderate efficacy in preserving femoral bone loss [80]. Although none of the studies was powered to estimate fracture risk efficacy, in some of them ETN reduced vertebral fracture incidence [80,134].

Three randomized comparative longitudinal studies compared ETN versus Ca+VitD for a period between 3 and 7 years [133-135]. Intermittent administration of ETN increased significantly lumbar BMD compared to the control group ($p < 0.01$) in 102 GC-treated patients for 3 years [135]. This effect was more evident in the postmenopausal women. Although fewer patients had new vertebral fractures in the ETN group compared to placebo (0 vs 2), this difference was no significant.

Sato *et al.* followed up their cohort of 102 Japanese patients who originally participated in a 3-year trial [135] for another 4 years [133]. ETN increased significantly lumbar BMD compared to placebo (5.9 vs 2.2%) ($p = 0.02$). ETN was more effective in increasing lumbar BMD in premenopausal women ($p = 0.001$) than in postmenopausal ($p = 0.23$). There was no however significant reduction in vertebral fracture risk at 7 years (odds ratio 3.000, $p = 0.18$).

5.2.2.2 *Pamidronate*

Pamidronate (PMN) is a nitrogen-containing BP that was effective in the primary prevention or treatment of GIOP in specific studies [78,79,136-142]; it demonstrated however differential outcomes related to the route of administration.

In a prospective randomized controlled trial [141], 40 patients receiving long-term GC therapy were randomly assigned to receive PMN (150 mg/day) plus calcium (1 g/day) or calcium alone. Oral PMN increased the mean metacarpal cortical area and the mean vertebral mineral density compared to placebo > 12 months ($p < 0.01$ and $p < 0.005$ respectively). At the end of the second year [142] the control group continued to lose bone mass in contrast to the PMN group that was stable. Lumbar BMD difference between groups was also significant at the end of the second year. In a highly selected cohort of 30 premenopausal female suffering from connective tissue disease (mostly Systemic Lupus Erythematosus) patients, taking

Table 1. Selected GIOP treatment randomized comparative studies.

Drug (Ref.) (dose/day/ route)	Comparator (CMP) (dose/day/ route)	Design	n	Sex	Underlying disease	GL (mg/day prednisolone or equivalent)	Ca/Vit D (dose per day)	Meno pausal status	Duration	Lumbar BMD change (%)		p	Femoral BMD change (%)		p	Vertebral fracture		P
										CMP	Drug		CMP	Drug		CMP	Drug	
CALC [107] 200 IU*	ALN 10 mg‡	Tμ	50	F	RA	Low dose	1 gr/400 IU	PoM	2 years	+4.34	+1.75	< 0.05	+2.52	-3.76	< 0.001	-	-	-
¶ETN [80] 400 mg‡	Placebo (Ca)	PR	141	M/F	Mainly RA/Po Rh	≥ 7.5	500 mg Ca	Mainly PoM	1 year	-3.23	+0.61	0.02	-1.67	+0.19	0.63	10/ 63	5/57	NS
¶ETN [135] 200 mg‡	Placebo (Ca/vitD)	Both	102	M/F	50% SLE	> 7.5	‡‡3.0 g/ 0.75 mg	Mainly PrM	3 years	+0.4	+4.8	< 0.01	-	-	-	3/31	0/30	NS
¶ETN [133] 200 mg‡	Placebo (Ca/vitD)	Both	91	M/F	50% SLE	> 7.5	‡‡3.0 g/ 0.75 mg	Mainly PrM	7 years	+2.2	+5.9	0.02	-	-	-	11/ 45	3/46	0.18
PAM [141] 150 mg‡	Placebo (Ca)	TM	40	M/F	Various	Mean dose 12-15	1 gr Ca	PrM/ PoM	1 year	-8.8	+19.6	< 0.005	-	-	-	-		-
PAM [142] 90 mg§	Placebo (Ca)	PR	32	M/F	Various	≥ 10	800 mg Ca	Mainly PoM	2 years	-4.6	+1.7	< 0.001	-3.1	+1.2	< 0.01	-		-
ALN [96] 5/10 mg‡	Placebo (Ca/vitD)	Both	477	M/F	Various	≥ 7.5	800 – 1000 mg/ 250 – 500 IU	PrM/ PoM	48 weeks	-0.4	+2.1/ +2.9	< 0.001	-1.2	+1.2/ +1.0	< 0.001	8/ 135	8/ 268	NS
ALN [116] 5/10 mg‡	Placebo (Ca/vitD)	Both	208	M/F	Mainly rheumatological	≥ 7.5	800 – 1000 mg/ 250 – 500 IU	PrM/ PoM	2 years	-0.77	+2.8/ +3.8	< 0.05	-2.93	+0.1/ +0.6	< 0.05	4/59	1/ 143	0.026
RSN [99] 2.5/5 mg‡	Placebo (Ca/vitD)	TM	290	M/F	Various (mainly RA)	≥ 7.5 (mean 15)	1 g/400 IU	Mainly PoM	1 years	+0.4	+1.9/ +2.9	< 0.001	-0.3	-0.2/ +1.8	0.004	9/60	6/60	0.04
RSN [81] 2.5/5 mg‡	Placebo (Ca/vitD)	PR	224	M/F	Various (RA. SLE,PR)	≥ 7.5	500 mg/ 500 IU	Mainly PoM	1 year	-2.8	-0.1/ +0.6	< 0.005 < 0.001	-3.1	-0.4/ +0.8	NS < 0.001	9/52	3/ 53#	0.07
RSN [117] 2.5/5 mg‡	Placebo (Ca/vitD)	Both	518	M/F	Various (40% RA)	Moderate to high	500 – 1000 mg/ 400 IU	Mainly PoM	1 year	-1.0	1.1/ 1.9	< 0.001	-1.5	-0.3/ +1.3	NS < 0.001	18/ 111	6/ 111	< 0.01
ZLN [98] 5 mg§	RSN 5 mg‡	TM	545	M/F	Various (40% RA, PR)	≥ 7.5	1 g/400 – 1200 IU	Mainly PoM	1 year	+2.71	+4.06	≤ 0.0001	+0.39	+1.45	≤ 0.005	3/ 417	5/ 416	NS
ZLN [98] 5 mg§	RSN 5 mg‡	PR	288	M/F	Various (40% RA, PR)	≥ 7.5	1 g/400 – 1200 IU	Mainly PoM	1 year	+0.64	+2.6	≤ 0.0001	-0.03	+1.3	≤ 0.0049			

Demographics, menopausal status, data on drug efficacy on BMD and vertebral fracture protection are presented.

*Intranasally/ ‡per os/ §intravenously/ ¶intermittent ETN for 14 days followed by Calcium administration for 76 days (4 cycles).

#Calcium lactate/alphacacidol.

**Not femoral neck but total hip.

‡‡Only 5 mg RSN group.

F: Female; M: Male; N/A: Not applicable; NS: Non-statistical significance; PoM: Postmenopausal; PR: Prevention; PrM: Premenopausal; RA: Rheumatoid arthritis; RP: Rheumatic Polymyalgia; SLE: Systemic lupus erythematosus; TM: Treatment.

Table 1. Selected GIOP treatment randomized comparative studies (continued).

Drug (Ref.) (dose/day/ route)	Comparator (CMP) (dose/day/ route)	Design	n	Sex	Underlying disease	GL (mg/day prednisolone or equivalent)	Ca/Vit D (dose per day)	Meno pausal status	Duration	Lumbar BMD change (%)		p	Femoral BMD change (%)		p	Vertebral fracture		P
										CMP	Drug		CMP	Drug		CMP	Drug	
ZLN [157] 5 mg[§]	RSN 5 mg[‡]	PR/TM	78/ 152	M	Various	≥ 7.5	1 g/400 –1200 IU	-	1 year	-0.24 +3.27	+2.46 +4.69	.0024 .023	-0.02 +0.38	+1.37 +1.31	0.08 0.17	-		-
IBN [161] 150 mg[‡]	Placebo (vit D/Ca)	PrR	140	F	Rheumatological	5 – 15 mg	800 mg/ 1000 IU	PoM	1 year	-0.1	+3.2	< 0.001	-0.6	+2.0	< 0.001	-		-
TRP [97] 20 mg[¶]	ALN 10 mg[‡]	TM	428	F/M	Various (mainly RA)	≥ 5	1 g/800 IU	Mainly PoM	18 months	+3.4	+7.2	< 0.001	+2.4**	+3.8**	0.005	10/ 165	1/ 171	0.004
TRP [163] 20 mg[¶]	ALN 10 mg[‡]	TM	277	F	Various (mainly RA)	≥ 5	1 g/800 IU	PoM	18 months	+3.7	+7.8	< 0.001	N/A	N/A	NS	6/ 111	1/ 106	0.05
TRP [163] 20 mg[¶]	ALN 10 mg[‡]	TM	67	F	Various (mainly RA)	≥ 5	1 g/800 IU	PrM	18 months	+0.7	+7.0	< 0.001	N/A	N/A	< 0.01	0/23	0/33	N/A
TRP [163] 20 mg[¶]	ALN 10 mg[‡]	TM	83	M	Various (mainly RA)	≥ 5	1 g/800 IU	-	18 months	+3.7	+7.3	0.03	N/A	N/A	NS	4/31	0/31	0.05
TRP [165] 20 mg[¶]	ALN 10 mg[‡]	TM	294	F/M	Various (mainly RA)	≥ 5	1 g/800 IU	Mainly PoM	36 months	+5.3	+11	< 0.001	+3.4	+6.3	< 0.001	13/ 169	3/ 173	0.007

Demographics, menopausal status, data on drug efficacy on BMD and vertebral fracture protection are presented.

*Intranasally/ [‡]per os/ [§]intravenously/ [¶]intermittent ETN for 14 days followed by Calcium administration for 76 days (4 cycles).

[#]Calcium lactate/alphacacidol.

**Not femoral neck but total hip.

[‡‡]Only 5 mg RSN group.

F: Female; M: Male; N/A: Not applicable; NS: Non-statistical significance; PoM: Postmenopausal; PR: Prevention; PrM: Premenopausal; RA: Rheumatoid arthritis; RP: Rheumatic Polymyalgia; SLE: Systemic lupus erythematosus; TM: Treatment.

Table 2. Scoring the drugs in relation to disease demographics and BMD/fracture protection status.

	Tr/Pr	PoM	PrM	Men	Duration of studies (years)	Lumbar BMD	Hip BMD	Vertebral fracture risk	Non vertebral fracture risk	In Comparison to
CALC [105-113]	Both	N/A	N/A	N/A	7	+	-	-	-	< ALN
ETN [80,133-135]	Both	+	+	+	7	+	±	-	-	N/A
PMN [78,79,141,142]	Both	N/A	N/A	N/A	2	+	+	-	-	N/A
ALN [96,97,116,118]	Both	+	+	+	2	+	+	±	-	< TRP
RIS [81,99,117,148]	Both	+	-	+	2	+	+	+	-	< ZOL
ZOL [98,156-158]	Both	+	±	+	1	+	+	-	-	> RSN
IBN [159-162]	N/A	+	N/A	N/A	3	+	+	±	-	N/A
TPTD [97,163-171]	TM	+	+	+	2	+	+	+	-	> ALN
D-Mab [174]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

<: Less effective; >: More effective; N/A: Not Applicable; PoM: Postmenopausal; PR: Prevention; PrM: Premenopausal; TM: Treatment.

high-dose GL therapy, 100 mg/day oral PMN maintained lumbar spine but not hip BMD for a year [138].

More interestingly i.v. PMN showed superior efficacy, not only in lumbar but also in femoral BMD improvement. No reduction of vertebral and non-vertebral fractures was reported. Studies extended maximum for 2 years and had very small sample size [78,79]. There was no comparative study to other antiosteoporotic drugs. PMN has also been studied and found to be safe and effective in specific pediatric populations suffering from nephropathy [137,139].

In a randomized annual placebo control trial [78] reported by Boutsen *et al.*, intermittent (i.v.) administration of disodium PMN and calcium p.os significantly increase compared to placebo the mean lumbar BMD (3.6 vs –5.3%) and femoral neck BMD (2.2 vs –5.3%, $p < 0.001$). In a further study a single 90 mg or an initial 90 mg followed by 30 mg every 3 months (i.v.) infusion of PMN prevented hip and lumbar spine bone loss in patients receiving long-term high GC doses [79]. At 1 year, both forms of PMN administration, significantly increased the mean lumbar spine BMD (1.7/2.3% respectively), femoral neck BMD (1.2/1.2% respectively) and total hip BMD (1.0/2.6% respectively). Although no significant difference was estimated between PMN groups, there was highly significant difference between them and control group concerning lumbar spine ($p < 0.001$), femoral neck ($p < 0.01$), and total hip ($p < 0.05$).

5.2.2.3 *Alendronate*

Randomized or not placebo-controlled studies have demonstrated that ALN was effective in the prevention and treatment of GIOP [96,102,116,118,143-147]. ALN was efficient not only in lumbar but also in femoral BMD improvement. Although the studies were unpowered to detect fracture diminishment, in some of them ALN reduced vertebral fracture risk [116]. Studies lasted maximum for 2 years and included patients suffering from various diseases and GC doses [146]. Both daily and weekly administration of ALN was effective [118]. ALN demonstrated however inferior efficacy compared to Teriparitide [97].

In the principal study, reported by Saag *et al.* [96] escalating oral doses (2.5 – 5.0 – 10.0 mg) of ALN were compared with placebo treatment on 560 GC-treated men and women. Patients were randomly assigned to receive 2.5, 5 or 10 mg ALN or placebo for 48 weeks. They all received calcium (800 – 1000 mg/day) and vitamin D (250 – 500 IU/day) supplements. 5 and 10 mg of ALN increased significantly the lumbar spine BMD and the femoral-neck bone density compared to baseline by 1.2% in 5 mg and 1.0% in 10 mg ALN group ($p < 0.01$) (2.1 and 2.9% respectively, $p < 0.001$). 5 and 10 mg ALN were more effective than placebo at all skeletal sites ($p < 0.001$). However this study was unpowered to detect differences in fracture risk.

In a 12-month extension of the latter trial [96], 166 patients completed 24 months evaluation [116]. Following 2 years of treatment, the mean lumbar BMD increased significantly compared to baseline, by 2.8 and 3.9%, respectively in the groups receiving 5 and 10 mg ($p < 0.001$). Patients that took any dose of ALN increased significantly trochanteric ($p < 0.05$) and maintained femoral neck bone density. 5 and 10 mg ALN were more effective than placebo at all skeletal sites ($p \leq 0.05$). At the end of the second year, there were significantly fewer patients with morphometrically vertebral fractures in all ALN-treated groups (0.7%) compared with the placebo (6.8%) ($p = 0.026$). Although the incidence of non-vertebral fractures was lower in the ALN group compared to placebo, this difference was not statistically significant.

In a retrospective, observational study asking the effect of ALN discontinuation Emkey *et al.* [143] evaluated GC-treated patients who had previously received 5 or 10 mg of ALN for a year [82]. There was significant decrease in the mean lumbar (5.1%) and femoral neck BMD (9.2%) of patients

discontinued to take ALN compared to the values at month 12. Patients, who took < 6 mg/day of prednisone during the follow-up period, demonstrated less and nonsignificant bone loss at lumbar spine and hip.

In a 18-month prospective randomized study aiming to detect the effect of ALN in premenopausal women [144] oral ALN and alfacacidol increased significantly the mean lumbar BMD (+1.7 vs –9.9%) and decrease the fracture rate (0 vs 4 fractures) compared to alfacacidol alone in 47 premenopausal women suffering from autoimmune diseases. ALN administered at 70 mg once weekly, proved to be also effective in GIOP. In a 12-month, randomized, double-blind, placebo-controlled trial reported by Stoch *et al.* [118]. ALN 70 mg once weekly significantly increased lumbar spine BMD (2.45%), trochanter BMD (1.27%), total hip BMD (0.75%) compared with baseline. ALN 70 mg was more effective than placebo at all skeletal sites ($p \leq 0.001$, $p = 0.007$, $p = 0.008$ respectively).

5.2.2.4 Risedronate

Risedronate (RIS) demonstrated efficacy in both lumbar and femoral BMD in treatment and prevention studies [81,99]. Powered RIS studies revealed also vertebral fracture risk efficacy [117]. Maximum follow up was for 2 years. Both daily and weekly administration of RIS appeared to be effective [148-155]. RIS effectiveness was independent of sex but it was related to menopausal status. RIS demonstrated however inferior efficacy compared to zoledronate in a comparative study [98].

There are two principal studies, one prevention and one treatment, concerning the use of RIS in GC-treated patients [81,99]. In a double-blind, placebo-controlled randomized study [99] different doses of RIS (2.5 – 5.0 mg) were compared to placebo on 290 men and women who were treated with high-dose oral GC therapy. 5 mg RIS significantly improved lumbar spine 2.9 ± 0.67% (mean ± SD) ($p = 0.05$), femoral neck 1.8 ± 0.67% ($p = 0.01$) and trochanter BMD 1.6 ± 0.81% ($p = 0.05$) compared to placebo. Although this study was not powered to estimate fracture risk efficacy, there were significantly fewer vertebral fractures in the whole RIS group compared to placebo (5 vs 15 %) ($p = 0.042$).

The other study [81] evaluated the efficacy of RIS therapy in the prevention of GIOP. In this randomized, double-blind, placebo-controlled study, 224 men and women who were initiating long-term GC treatment were randomized to receive either oral RIS (2.5 mg or 5 mg) or placebo daily for 12 months. 5-mg RIS significantly increased lumbar spine BMD (3.8 ± 0.8%), femoral neck (4.1 ± 1.0%) and femoral trochanter BMD (4.6 ± 0.8%) compared to placebo ($p < 0.001$ at all sites). 2.5 mg RIS was significantly more effective at lumbar spine (3.0 ± 0.9%) ($p = 0.003$) and trochanter (3.6 ± 1.2%) ($p = 0.004$) compared to placebo. This study was not powered to detect fracture risk reduction. Fewer vertebral fractures occurred however in the 5 mg RIS compared to the placebo group (5.7 vs 17.3%, $p = 0.072$).

A post hoc analysis of the latter two studies was powered to assess fracture incidence [117]. 5 mg RIS was more effective than placebo at all skeletal sites ($p \leq 0.001$). 2.5 mg RIS demonstrated less efficacy than 5 mg RIS. RIS increased significantly the mean lumbar BMD in postmenopausal women and men compared to placebo but had less and nonsignificant effect in premenopausal women. RIS was efficient independently of underlying disease and duration of GC therapy. 2.5 and 5 mg RIS reduced significantly the vertebral fracture risk by 58 and 70% respectively compared to placebo ($p = 0.01$ and $p = 0.08$).

In another post hoc analysis of the two principal studies, Reid *et al.* [148] evaluated the efficacy of RIS in 184 GC-treated male patients. In the treatment study, 5 mg RIS significantly increased lumbar, femoral neck and trochanter BMD compared to placebo ($p < 0.01$). In the prevention study, 5 mg RIS significantly prevented bone loss compared to placebo ($p < 0.001$). 2.5 mg RIS was less effective than 5 mg in both studies. The RIS group experienced 82% less vertebral fractures compared to placebo ($p = 0.008$).

Several other studies [149-155] evaluated the effect of RIS in GIOP. In a 2 year, double-masked, placebo-controlled randomized trial Eastell *et al.* [149] evaluated 2.5 mg/day oral RIS or cyclical 15 mg RIS (15 mg oral RIS daily during 2 weeks followed by placebo daily during 10 weeks) in 120 GC-treated postmenopausal women with Rheumatoid Arthritis. At the end of the second year, BMD was preserved at the lumbar spine (+1.4%) and trochanter (+0.4%) but declined at the femoral neck in the daily 2.5 mg RIS group ($p = 0.03$ and $p > 0.05$ respectively). The differences between 2.5 mg RIS and placebo were significant at all skeletal sites except femoral neck. Cyclical RIS appeared less efficacious than daily 2.5 mg RIS at the lumbar spine. There was no difference in the incidence of vertebral fractures between groups. Using data from 11.007 women ≥ 65 years taking GC Thomas *et al.* [151] estimated that ALN significantly reduced fracture incidence at 15 months of therapy compared to 3 months (33% at non-vertebral sites and 59% at vertebral sites) and also did RIS (28% at non-vertebral sites and 54% at vertebral sites).

Once weekly RIS 35 mg proved to be also effective in GIOP. In a randomized placebo-controlled study [153]. RIS 35 mg once weekly prevented more effectively bone loss compared to placebo in 78 patients following an 8-week course of prednisolone given for an exacerbation of inflammatory bowel disease. There were no significant differences however between placebo and RIS groups at lumbar spine and total hip.

5.2.2.5 Zoledronate

Intravenous zoledronate (ZOL) is an approved drug for both prevention and treatment of GIOP [98,156-158]. In a 1-year study ZOL was superior to RIS in increasing lumbar and femoral BMD; no fracture risk reduction however was reported [98].

HORIZON (Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly) was an 1-year, multicenter, double-blind, stratified, randomized controlled trial comparing one 5 mg i.v. infusion of ZOL to 5 mg oral daily dose of RIS for the prevention and treatment of GIOP [98]. 545 patients that had been taking at least 7.5 mg/day oral prednisolone (or equivalent) within the last 3 months enrolled in the treatment subgroup whether 288 that had been taking GC ≥ 3 months enrolled in the prevention subgroup. All patients received 1000 mg/day/per os calcium and 400 – 1.200 IU vitamin D3. Following 12 months of therapy, ZOL was superior to RIS in increasing the lumbar spine BMD in both the treatment (mean difference/m.d. 1.36%, p = 0.0001) and prevention subgroups (mean difference 1.96%, p < 0.0001). ZOL also increased significantly the BMD at the femoral neck compared with RIS, in both the treatment (m.d. 1.06%, p < 0.005) and prevention (m.d. 1.33%, p < 0.0049) subgroups. There was no significant difference however in the incidence of new vertebral fractures between groups. Adverse events were more common in the ZOL group but only during the first 3 days after the infusion [98].

In a post hoc analysis of HORIZON study [156] Roux *et al.* reported that ZOL increased more efficiently lumbar BMD than RIS in the age groups 35 – 50 years (p = 0.0041), 51 – 64 years (p = 0.0075), 65 – 74 years (p = 0.0294) of the treatment group and in the 65 – 74 years subgroup (p = 0.0008) of the prevention group. ZOL reduced significantly lumbar BMD loss in both male (p < 0.05) and female (p < 0.01), in patients having baseline 25-OH vitamin D concentrations > 20 ng/ml (p < 0.01) and in postmenopausal women (p < 0.05) at 12 months for both groups. ZOL also demonstrated superior efficacy in patients with a mean prednisone dose of 7.5 – 12 mg/day during the trial (p < 0.0001) and in patients with a baseline creatinine clearance of ≥ 60 ml/min (p < 0.0001 groups). ZOL was more efficient than RIS in increasing lumbar BMD in osteoporotic patients of prevention group (p = 0.0189) and in osteopenic patients of the treatment group (p = 0.0305) [156].

In another post hoc analysis of HORIZON study, Sambrook *et al.* reported efficacy of ZOL in men subpopulation [157]. At 12 months ZOL increased significantly the lumbar BMD compared to RIS in both the prevention (m.d. 2.7%, p = 0.0024) and the treatment groups (m.d. 1.42%, p = 0.0232) and the total hip BMD in both the prevention (m.d. 1.49%, p = 0.0230) and treatment subpopulation (m.d. 1.65%, p = 0.0004). Femoral neck BMD was non-significantly different between groups.

5.2.2.6 Ibandronate

Ibandronate (IBN) is a nitrogen containing BP demonstrating usefulness in the clinical management of GIOP. It is less studied compared with other BP [159-162]. In a 3 year trial, Ringe *et al.* [159] compared the efficacy of every 3 months i.v. IBN with daily oral alfacalcidol (1 microg) in 115 GC-treated patients. Although both treatments were effective, IBN increased significantly more the mean lumbar BMD (13.3 vs 2.6%, respectively; p < 0.001) and femoral neck BMD (5.2 vs 1.9%, respectively; p < 0.001) compared to alfacacidol. Following 3 years of treatment, IBN also reduced significantly the vertebral fracture risk compared to alfacacidol therapy (8.6 vs 22.8%, respectively; p = 0.043) and back pain of patients (p < 0.001). This study however was unpowered to detect differences in fracture incidence. Despite the small sample size, Fahrleitner-Pammer *et al.* [162] reported also that IBN was effective in preventing lumbar BMD and reducing vertebral fractures compared to placebo in 35 heart transplant recipients [162].

In another randomized, double-blind, placebo-controlled prevention study Hakala *et al.* [161] studied 140 GC-treated postmenopausal women. Patients were randomly allocated to receive either monthly 150 mg oral IBN or placebo for 12 months. IBN increased significantly the mean lumbar (3.2%), trochanter, femoral neck and total hip BMDs compared to baseline at 12 months. However only lumbar BMD increase was significant (p < 0.001) than placebo.

5.2.3 Teriparatide

Teriparatide (TPTD) is an anabolic therapy that was evaluated mainly in the treatment of GIOP. It was efficient in lumbar and in femoral BMD improvement. In powered studies it demonstrated efficacy in vertebral fracture risk reduction [97]. Studies lasted maximum for 36 months and included patients suffering from various diseases [97,163-171]. Furthermore TPTD demonstrated superior treatment efficacy in lumbar and hip BMD and vertebral fracture reduction compared to ALN [97].

In an 18-month randomized, double-blind, controlled trial, Saag *et al.* [97] evaluated 428 women and men with osteoporosis that received GC for at least 3 months (prednisone 5 mg/day or more). Patients were randomly assigned to receive 20 microg/day injectable (inj) TPTD (n = 214) or 10 mg ALN once daily (n = 214). All patients took also 1000 mg of elemental calcium/day and 800 IU vitamin D/day. Participants suffered from lower BMD and more prevalent fractures than patients in other GIOP trials. At 18 months, TPTD demonstrated significant greater increase in lumbar BMD (7.2 ± 0.7%) compared to ALN (3.4 ± 0.7%) (p < 0.001). TPTD was also significantly more effective in total hip BMD compared to ALN (m.d. 1.4%, p = 0.005). Although the study was not powered to assess vertebral fracture risk reduction, there were significantly fewer new vertebral fractures in the TPTD than in the ALN group (0.6 vs 6.1%, p = 0.004); the non-vertebral fracture incidence however did not differ between groups (5.6 vs 3.7%, p = 0.36). Although there were no significant differences in the overall incidence of adverse events between groups, the occurrence of sporadic hypercalcaemia was more frequent in the TPTD group. It should be emphasized that 31.3% of patients discontinued from the study due to the severity of underlying illnesses.

In a subgroup analysis of the previous study [97], Langdahl *et al.* [163] evaluated the effect of gender and menopausal status on TPTD efficacy. At 18 months, TPTD demonstrated significantly greater mean lumbar BMD increase from baseline compared to ALN in postmenopausal women (7.8 vs 3.7%, $p < 0.001$), premenopausal women (7.0 vs 0.7%, $p < 0.001$) and men (7.3 vs 3.7%, $p = 0.03$). Although TPTD showed better efficacy in hip BMD than ALN in all groups, this reached statistical significance only in premenopausal women ($p < 0.01$). There were significantly fewer vertebral fractures in the TPTD group for postmenopausal women (1 vs 6, $p = 0.05$) and men (0 vs 4, $p = 0.05$), but no difference in premenopausal women and non-vertebral fractures for all subgroups.

In another post hoc analysis of Saag's study [97], Devogealer *et al.* [164] evaluated the effect of baseline GC dose on the 18-month BMD treatment response in 387 GC-treated patients. The mean baseline GC dose was classified as low (< or = 5 mg/day), medium (> 5 and < 15 mg/day), or high (> or = 15 mg/day). TPTD and ALN significantly increased from baseline the lumbar, femoral neck and total hip BMD of patients taking low and medium baseline GC at 18 months. Furthermore TPTD increased significantly lumbar BMD of patients receiving low and medium GC doses compared to ALN (mean difference 3.6%, $p < 0.001$). TPTD however was significantly less efficient in lumbar BMD increase in high GC compared the low GC dose group (m.d. 3.5%, $p = 0.0012$). The overall femoral neck and total hip BMD effect was not different between treatments.

The principal study [97] was further extended for 18 months [165]. TPTD increased significantly baseline BMD compared to the ALN at 36 months, at the lumbar spine (11.0 vs 5.3%), total hip (5.2 vs 2.7%) and the femoral neck (6.3 vs 3.4%) ($p < 0.001$ for all). Following 36 months of therapy, significantly fewer patients had vertebral fractures in the TPTD than in the ALN group (3/173 (1.7%) versus 13/169 (7.7%); $p = 0.007$). There was no significant difference between groups in the incidence of non-vertebral fractures (16 vs 15 respectively = 0.843). Although there was no difference in the incidence of serious adverse events between groups, significantly more patients in the TPTD group had elevated predose serum calcium concentrations (21 vs 7%) ($p < 0.001$). Subject discontinuation rate continued to be high (44%). TPTD induced significantly greater changes from baseline in biochemical markers of bone formation (P1NP) ($p < 0.001$) and resorption (C-terminal telopeptide of type 1 collagen [CTX]) ($p < 0.001$) in comparison to the ALN [166]. The lumbar spine and femoral neck BMD increase at 18 months in the TPTD group were significantly correlated with PINP increase at 1 and 6 months ($p < 0.05$) and negatively correlated with change in Sbeta-CTX at 1 month ($p < 0.05$) [167].

Several other studies evaluated the efficacy and safety of TPTD in the GIOP treatment [168-171]. In a prospective, multinational, observational study Karras *et al.* [168] assessed the effectiveness of 18 month TRP therapy in 294 GC users. There was reduction of clinical fractures incidence ($p < 0.05$) and back pain and improvement of the quality of life during the third year of sequential osteoporosis medication (mainly BP) compared with the first 6 months. TPTD demonstrated also superior efficacy than hormone replacement therapy in postmenopausal women receiving GC [171]. TPTD and estrogen significantly increased lumbar BMD compared to estrogen alone ($p < 0.001$).There were no differences in hip and forearm bone density between groups.

5.2.4 *Strontium ranelate*

Strontium ranelate (SR) has not been widely studied in the treatment of GIOP. To the best of our knowledge no clinical data of SR on GIOP exist. In a 9-week experimental study in GC treated rats, Sun *et al.* [172] demonstrated greater efficacy of SR compared to ALN in femoral diaphysis and fifth vertebra BMD increase and histomorphometrical characteristics of cancellous and cortical bone.

5.2.5 *Denosumab*

GC amplify the expression of M-CSF and RANK-L in stromal and osteoblastic cells [23,48] and suppress osteoclast's apoptosis, through inhibition of the soluble decoy receptor of RANKL, osteoprotegerin (OPG) [19]. Consequently RANKL inhibition mediated via Denosumab (D-Mab), a monoclonal antibody against RANKL, could be preferable in GC-treated patients.

D-Mab prevented bone loss and improved biomechanical compression tests of lumbar vertebrae in 8-month-old homozygous hRANKL – knockin mice treated for a month with prednisolone (2.1 mg/kg) [173]. One clinical study till now evaluated the efficacy of D-Mab in GC-treated patients [174]. In a double-blind, placebo-controlled, Phase II study, 218 GC-treated RA patients were randomly allocated to receive D-Mab 60 mg (n = 71), D-Mab 180 mg (n = 75) or placebo (n = 75) at baseline and 6 months. Denosumab proved to efficiently increase mean lumbar and femoral BMD and also reduce sCTX at 12 months compared to placebo.

6. Expert opinion

The selection for treating a GC-patient remains controversial. Several treatment guidelines have been proposed; however none of them is widely accepted. Among others the use of FRAX or BMD and the dose and duration of GC administration for treatment initiation have not been clarified. In the majority of the available published literature indication for treatment is daily dose of at least 7.5 mg prednisolone for 3 months in postmenopausal or osteopenic premenopausal women and men.

It seems however necessary that there should be a more individualized patient selection for GIOP management; rigid selection criteria appeared to be ambiguous. The patient's past

Table 3. Selected GIOP treatment randomized comparative studies.

Drug (ref)	Comparator (CMP)	Sex	Meno pausal status	Lumbar BMD change (%)	p value‡	Femoral BMD change (%)	p value‡	Vertebral fracture	p value‡
ALN [116]	Placebo (Ca/ vitD)	M/F	PrM/PoM	+2.8/+3.8	< 0.05	+0.1/+0.6	< 0.05	1/143	0.026
RSN [117]	Placebo (Ca/ vitD)	M/F	Mainly PoM	1.1/1.9	< 0.001	-0.3/+1.3	NS < 0.001	6/111	< 0.01
ZLN [98]	RSN	M/F	Mainly PoM	+4.06	≤ 0.0001	+1.45	≤ 0.005		
ZLN [98]	RSN	M/F	Mainly PoM	+2.6	≤ 0.0001	+1.3	≤ 0.0049	5/416	NS
IBN [161]	Placebo (vit D/Ca)	F	PoM	+3.2	< 0.001	+2.0	< 0.001	-	-
TRP [97]	ALN	F/M	Mainly PoM	+7.2	< 0.001	+3.8*	0.005	1/171	0.004
TRP [163]	ALN	F	PoM	+7.8	< 0.001	N/A	NS	1/106	0.05
TRP [163]	ALN	F	PrM	+7.0	< 0.001	N/A	< 0.01	0/33	N/A
TRP [165]	ALN	F/M	Mainly PoM	+11	< 0.001	+6.3	< 0.001	3/173	0.007

Comparative data on drug efficacy on BMD and vertebral fracture protection in pre-and postmenopausal women are presented.
*Not femoral neck but total hip. ‡Compared to CMP.
F: Female; M: Male; N/A: Not Applicable; NS: Non statistical significance; PoM: Postmenopausal; PrM; Premenopausal.

medical history and age, menopausal status, the underlying disease, the GC dose and duration and the anticipated duration of administration could be key points in the selection of patients to treat. Treatment should be considered certainly in patients at high risk of fracture, elderly or with very low BMD value or patients receiving very high GC dose.

GC-treated patients must comply to a healthy lifestyle. They should maintain normal body weight and follow daily balance exercises. Additionally they should cease smoking and avoid drink consumption. Supplemental Ca and Vit D have a place in the management of GIOP. Vit D alone and combined Ca/vit D demonstrated efficacy in increasing lumbar BMD but not fracture risk reduction. Ca/vit D had synergistic effect when coadministered with other more potent drugs and they could be regarded as adjuvant therapy in GIOP management. The daily Ca and vitamin D intake have to exceed the corresponding intake in PMO. GC-treated patients should receive 500 – 1000 mg Ca and at least 800 mg vit D per os daily. Although active metabolites of vit D may be more efficacious in BMD reduction than native vit D they have not demonstrated superior efficacy in vertebral fracture reduction.

The limited evidence (power and duration) of GIOP studies has not clarified so far the first choice of treatment in GC-treated patients. BP therapy seems to be the current standard of care for prevention and treatment of GIOP. The data suggest also that primary prevention is more efficacious than treatment thus starting GC treatment for more than 3 months and a dose of a minimum of 7.5 mg of prednisolone or equivalent should immediately raise the question of initiating BP prevention treatment. Most of BP demonstrated a significant treatment effect on lumbar BMD increase for 2 years (**Table 1**). ETN however was efficient in lumbar BMD maintenance for nearly 7 years of treatment. Hip BMD however was less affected by the use of BP. ETN most often failed to provide a significant beneficial effect on hip BMD whereas PMN, ALN, RIS and ZOL performed better on hip BMD. Regarding vertebral anti-fracture efficacy increasing volume of evidence supports of the use of specific BP namely ALN, RIS and ZOL in postmenopausal women and men (**Table 2**). This was mainly demonstrated in post hoc analyses of BP studies and by pooling several small sampled studies together. However none of them demonstrated efficacy in non-vertebral fracture reduction. ALN and RIS have been studied in RCTs in high GC dose-treated patients. Scarce data compare head-to-head BP efficacy; ZOL alone, in a small 1 year study, demonstrated superior efficacy in increasing lumbar and hip BMD compared to RIS. The clinical relevance of this effect could be questioned as this one year study did not show vertebral risk reduction with ZOL therapy. ZOL showed also a faster, more substantial inhibitory effect on bone turnover biomarkers than did RIS. This effect might be important for the prevention of GIOP because the BMD and the relevant increased of fracture risk can occur within a few months of GIOP treatment. Clinical data of IBN, D-Mab and SR are incomplete or unexisting. Further evidence is needed for these drugs.

BPs and Ca+Vit D have an anti-catabolic effect on bone. Balancing the anticatabolic effect of BPs against bone fragility caused by their chronic use remains unsolved. Newer bone anabolic approached using TPTD may address the latter limitation; thus potentially would have been proposed as the first

choice treatment. TPTD however is limited by the 24-month administration license and the lack of longitudinal efficacy data. TPTD however is an anabolic therapy that demonstrated superior efficacy in increasing lumbar and hip BMD and vertebral fracture reduction than ALN for 2 years. TPTD efficacy was evident mainly in the treatment of severe risk GC-treated patients. For the reasons above, in GC-treated patients at high risk of fracture with low BMD receiving long-term GC therapy TPTD could even be considered first choice of treatment. Major concern remains however the limit of 2 years maximum in the TPTD treatment.

An additional important denominator of GIOP treatment is the menopausal status of the patient. The effect of BP is usually better in postmenopausal compared to premenopausal women, probably due to their antiresorptive action. In addition administration of BPs in childbearing women carries the significant risk of potential fetal developmental complications, thus limiting their use in the latter group. Following 48 weeks of therapy with 10 mg/day ALN, lumbar spine BMD increased by 2.0% in premenopausal and 4.0% in postmenopausal women. In contrast, TPTD demonstrated comparable lumbar BMD increase in premenopausal (7.0%) and postmenopausal women (7.8%) (**Table 3**). Bone loss following GC therapy is primarily due to decreased bone formation. Thus the anabolic action of TPTD compared to the antiresorptive action of BP seems to have better results in GIOP.

The duration of therapy in GIOP is another critical issue as the majority of studies lasted for no more than 2 years. We certainly need more data on long-term GIOP treatment. Based on PMO studies, BP therapy could not be stopped if patient receives > 5 mg of GC.

Patient-specific treatment remains the cold standard of care. Early antiresorptive treatment in post-menopausal women appears to be efficient and safe. In the case however of premenopausal women and men with high fracture risk, TPTD may be adviced alternatively.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Seibel MJ, Cooper MS, Zhou H. Glucocorticoid-induced osteoporosis: mechanisms, management, and future perspectives. Lancet Diabetes Endocrinol 2013;1:59-70
2. Devogelaer JP, Goemaere S, Boonen S, et al. Evidence-based guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis: a consensus document of the Belgian Bone Club. Osteoporos Int 2006;17:8-19
3. Weinstein RS. Clinical practice. Glucocorticoid induced bone disease. N Engl J Med 2011;365:62-70
4. Hansen KE, Wilson HA, Zapalowski C, et al. Uncertainties in the prevention and treatment of glucocorticosteroid induced osteoporosis. J Bone Miner Res 2011;26:1989-96
5. Van Staa TP, Leufkens HG, Abenhaim L, et al. Use of oral corticosteroids in the United Kingdom. QJM 2000;93:105-11
6. Van Staa TP, Leufkens HG, Abenhaim L, et al. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000;15:993-1000
7. Adler RA. Glucocorticoid-induced osteoporosis: management update. Curr Osteoporos Rep 2010;8:10-14
8. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int 2007;18:1319-28
9. Kanis JA, Johansson H, Oden A, et al. A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 2004;19:893-9
10. Reid IR, Evans MC, Wattie DJ, et al. Bone mineral density of the proximal femur and lumbar spine in glucocorticoid-treated asthmatic patients. Osteoporos Int 1992;2:103-5
11. Stevens A, Ray DW, Zeggini E, et al. Glucocorticoid sensitivity is determined by a specific glucocorticoid receptor haplotype. J Clin Endocrinol Metab 2004;89:892-7
12. Warriner AH, Saag KG. Prevention and treatment of bone changes associated with exposure to glucocorticoids. Curr Osteoporos Rep 2013;11:341-7
13. Majumdar SR, Lix LM, Yogendran M, et al. Population-based trends in osteoporosis management after new initiations of long-term systemic glucocorticoids (1998-2008). J Clin Endocrinol Metab 2012;97:1236-42
14. Chitre MM, Hayes W. 3-year results of a member and physician intervention to reduce risk associated with glucocorticoid induced osteoporosis in a health plan. J Manag Care Pharm 2008;14:281-90
15. Solomon DH, Katz JN, La Tourette AM, Coblyn JS. Multifaceted intervention to improve rheumatologists' management of glucocorticoid-induced osteoporosis: a randomized controlled trial. Arthritis Rheum 2004;51:383-7
16. Van Staa TP, Laan RF, Barton IP, et al. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum 2003;48:3224-9
17. Buttgereit F, Burmester GR, Straub RH, et al. Exogenous and endogenous glucocorticoids in rheumatic diseases. Arthritis Rheum 2011;63:1-9
18. Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone 2004;35:375-82
19. Rizzoli R, Adachi JD, Cooper C, et al. Management of glucocorticoid-induced osteoporosis. Calcif Tissue Int 2012;91:225-43

20. Prummel MF, Wiersinga WM, Lips P, et al. The course of biochemical parameters of bone turnover during treatment with corticosteroids. J Clin Endocrinol Metab 1991;72:382-6

21. Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. J Clin Invest 1998;102:274-82

22. Bultink IEM, Baden M, Lems WF. Glucocorticoid-induced osteoporosis: an update on current pharmacotherapy and future directions. Expert Opin Pharmacother 2013;14:185-97

23. Compston J. Management of glucocorticoid-induced osteoporosis. Nat Rev Rheumatol 2010;6:82-8

24. Ohnaka K, Tanabe M, Kawate H, et al. Glucocorticoid suppresses the canonical Wnt signal in cultured human osteoblasts. Biochem Biophys Res Commun 2005;329:177-81

25. Westendorf JJ, Kahler RA, Schroeder TM. Wnt signaling in osteoblasts and bone diseases. Gene 2004;341:19-39

26. Wang FS, Ko JY, Yeh DW, et al. Modulation of Dickkopf-1 attenuate glucocorticoid induction of osteoblast apoptosis, adipocytic differentiation, and bone mass loss. Endocrinology 2008;149:1793-801

27. Hayashi K, Yamaguchi T, Yano S, et al. BMP/Wnt antagonists are upregulated by dexamethasone in osteoblasts and reversed by alendronate and PTH: potential therapeutic targets for glucocorticoid- induced osteoporosis. Biochem Biophys Res Commun 2009;379:261-6

28. Yao W, Cheng Z, Busse C, et al. Glucocorticoid excess in mice results in early activation of osteoclastogenesis and adipogenesis and prolonged suppression of osteogenesis: a longitudinal study of gene expression in bone tissue from glucocorticoid-treated mice. Arthritis Rheum 2008;58:1674-86

29. Den Uyl D, Bultink IE, Lems WF. Advances in glucocorticoid- induced osteoporosis. Curr Rheumatol Rep 2011;13:233-40

30. Glass DA, Bialek P, Ahn JD, et al. Canonical Wnt signaling in differentiated osteoblasts controls osteoclast differentiation. Dev Cell 2005;8:751-64

31. Smith E, Frenkel B. Glucocorticoids inhibit the transcriptional activity of LEF/TCF in differentiating osteoblasts in a glycogen synthase kinase-3beta-dependent and –independent manner. J Biol Chem 2005;280:2388-94

32. Ito S, Suzuki N, Kato S, et al. Glucocorticoids induce the differentiation of a mesenchymal progenitor cell line, ROB-C26 into adipocytes and osteoblasts, but fail to induce terminal osteoblast differentiation. Bone 2007;40:84-92

33. Pereira RC, Delany AM, Canalis E. Effects of cortisol and bone morphogenetic protein-2 on stromal cell differentiation correlation with CCAAT-enhancer binding protein expression. Bone 2002;30:685-91

34. Pereira RC, Delany AM, Canalis E. CCAAT/enhancer binding protein homologous protein (DDIT3) induces osteoblastic cell differentiation. Endocrinology 2004;145:1952-60

35. Canalis E. Effect of glucocorticoids on type I collagen synthesis, alkaline phosphatase activity, and deoxyribonucleic acid content in cultured rat calvariae. Endocrinology 1983;112:931-9

36. Canalis E. Mechanisms of glucocorticoid action in bone. Curr Osteoporos Rep 2005;3:98-102

37. Wu Z, Bucher NLR, Farmer SR. Induction of peroxisome proliferator-activated receptor g during the conversion of 3T3 fibroblasts into adipocytes is mediated by C/EBPh, C/EBPy, and glucocorticoids. Mol Cell Biol 1996;16:4128-36

38. O'Brien CA, Jia D, Plotkin LI, et al. Glucocorticoids act directly on osteoblasts and osteocytes to induce their apoptosis and reduce bone formation and strength. Endocrinology 2004;145:1835-41

39. Yun SI, Yoon HY, Jeong SY, Chung YS. Glucocorticoid induces apoptosis of osteoblast cells through the activation of glycogen synthase kinase 3beta. J Bone Miner Metab 2009;27:140-8

40. Bellido T. Antagonistic interplay between mechanical forces and glucocorticoids in bone: a tale of kinases. J Cell Biochem 2010;111:1-6

41. Plotkin LI, Manolagas SC, Bellido T. Glucocorticoids induce osteocyte apoptosis by blocking focal adhesion kinase-mediated survival: evidence for inside-out signaling leading to anoikis. J Biol Chem 2007;282:24120-30

42. Xia X, Kar R, Gluhak-Heinrich J, et al. Glucocorticoid-induced autophagy in osteocytes. J Bone Miner Res 2010;25:2479-88

43. Rochefort GY, Benhamou CL. Osteocyte are not only mechanoreceptor cells. Int J Numer Method Biomed Eng 2013;10):1082-8

44. Rochefort GY, Pallu S, Benhamou CL. Osteocyte: the unrecognized side of bone tissue. Osteoporosis Int 2010;21:1457-69

45. Lane NE, Yao W, Balooch M, et al. Glucocorticoid-treated mice have localized changes in trabecular bone material properties and osteocyte lacunar size that are not observed in placebo-treated or estrogen-deficient mice. J Bone Miner Res 2006;21:466-76

46. Jia D, O'Brien CA, Stewart SA, et al. Glucocorticoids act directly on osteoclasts to increase their life span and reduce bone density. Endocrinology 2006;147:5592-9

47. Teitelbaum SL. Bone resorption by osteoclasts. Science 2000;289:1504-8

48. Hofbauer LC, Gori F, Riggs BL, et al. Stimulation of osteoprotegerin ligand and inhibition of osteoprotegerin production by glucocorticoids in human osteoblastic lineage cells: potential paracrine mechanisms of glucocorticoid-induced osteoporosis. Endocrinology 1999;140:4382-9

49. Kondo T, Kitazawa R, Yamaguchi A, Kitazawa S. Dexamethasone promotes osteoclastogenesis by inhibiting osteoprotegerin through multiple levels. J Cell Biochem 2008;103:335-45

50. Dovio A, Perazzolo L, Saba L, et al. High-dose glucocorticoids increase serum levels of soluble IL-6 receptor alpha and its ratio to soluble gp130: an additional mechanism for early increased bone resorption. Eur J Endocrinol 2006;154:745-51

51. Kim HJ, Zhao H, Kitaura H, et al. Glucocorticoids suppress bone formation via the osteoclast. J Clin Invest 2006;116:2152-60

52. Schakman O, Kalista S, Barbé C, et al. Glucocorticoid-induced skeletal muscle atrophy. Int J Biochem Cell Biol 2013;45:2163-72

53. Natsui K, Tanaka K, Suda M, et al. High-dose glucocorticoid treatment induces rapid loss of trabecular bone mineral density and lean body mass. Osteoporos Int 2006;17:105-8

54. Delany AM, Gabbitas BY, Canalis E. Cortisol down regulates osteoblast 1(I) procollagen mRNA by transcriptional and post-transcriptional mechanisms. J Cell Biochem 1995;57:488-94

55. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 2002;13:777-87

56. Abadie EC, Devogealer JP, Ringe JD, et al. Recommendations for the registration of agents to be used in the prevention and treatment of glucocorticoid-induced osteoporosis: updated recommendations from the Group for the Respect of Ethics and Excellence in Science. Semin Arthritis Rheum 2005;35:1-4

57. Cooper MS, Rabbitt EH, Goddard PE, et al. Osteoblastic 11beta-hydroxysteroid dehydrogenase type 1 activity increases with age and glucocorticoid exposure. J Bone Miner Res 2002;17:979-86

58. Russcher H, Smit P, van den Akker EL, et al. Two polymorphisms in the glucocorticoid receptor gene directly aff ect glucocorticoid-regulated gene expression. J Clin Endocrinol Metab 2005;90:5804-10

59. Venuturupalli SR, Sacks W. Review of new guidelines for the management of glucocorticoid induced osteoporosis. Curr Osteoporos Rep 2013;11:357-64

60. Nawata H, Soen S, Takayanagi R, et al. Guidelines on the management and treatment of glucocorticoid induced osteoporosis of the Japanese Society for Bone and Mineral Research (2004). J Bone Miner Metab 2005;23:105-9

61. Adler RA, Hochberg MC. Suggested guidelines for evaluation and treatment of glucocorticoid-induced osteoporosis for the Department of Veterans Affairs. Arch Intern Med 2003;163:2619-24

62. Lekamwasam S, Adachi JD, Agnusdei D, et al. A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. Osteoporos Int 2012;23:2257-76

63. Pereira RM, Carvalho JF, Paula AP, et al. Guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis. Rev Bras Reumatol 2012;52:580-93

64. Geusens PP, Suzuki Y, Nawata H, et al. Guidelines on the management and treatment of the glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research: 2014 update. J Bone Miner Metab 2014;32(4):337-50

65. Geusens PP, de Nijs RN, Lems WF, et al. Prevention of glucocorticoid osteoporosis: a consensus document of the Dutch Society for Rheumatology. Ann Rheum Dis 2004;63:324-5

66. Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res 2010;62:1515-26

•• **American College of Rheumatology guidelines for GIOP management.**

67. Kanis JA, Johnell O, Oden A, et al. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 2008;19:385-97

68. Deal CL. Recent recommendations on steroid-induced osteoporosis: more targeted, but more complicated. Cleve Clin J Med 2013;80:117-25

• **Recent recommendations of American College of Rheumatology for GIOP management.**

69. Kanis JA, Johansson H, Oden A, McCloskey EV. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporos Int 2011;22:809-16

70. Lekamwasam S, Adachi JD, Agnusdei D, et al. A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. Osteoporos Int 2012;23:2257-76

71. Leib ES, Saag KG, Adachi JD, et al. Official positions for FRAX ((R)) clinical regarding glucocorticoids: the impact of the use of glucocorticoids on the estimate by FRAX((R)) of the 10 year risk of fracture from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX (R). J Clin Densitom 2011;14:212-19

•• **2012 International Osteoporosis Foundation and Calcified Tissue Society guidelines for GIOP management.**

72. Laan RF, van Riel PL, van de Putte LB, et al. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. Ann Intern Med 1993;119:963-8

73. Schakman O, Gilson H, Thissen JP. Mechanisms of glucocorticoid-induced myopathy. J Endocrinol 2008;197:1-10

74. Gluck OS, Murphy WA, Hahn TJ, Hahn B. Bone loss in adults receiving alternate day glucocorticoid therapy. A comparison with daily therapy. Arthritis Rheum 1981;24:892-8

75. Frediani B, Falsetti P, Bisogno S, et al. Effects of high dose methylprednisolone pulse therapy on bone mass and biochemical markers of bone metabolism in patients with active rheumatoid arthritis: a 12-month randomized prospective controlled study. J Rheumatol 2004;31:1083-7

76. Perez AV, Picotto G, Carpentieri AR, et al. Minireview on regulation of intestinal calcium absorption. Emphasis on molecular mechanisms of transcellular pathway. Digestion 2008;77:22-34

77. Ritz E, Kreusser W, Rambausek M. Effects of glucocorticoids on calcium and phosphate excretion. Adv Exp Med Biol 1984;171:381-97

78. Boutsen Y, Jamart J, Esselinckx W, et al. Primary prevention of glucocorticoid-induced osteoporosis with intermittent intravenous pamidronate: a randomized trial. Calcif Tissue Int 1997;61:266-71

79. Boutsen Y, Jamart J, Esselinckx W, Devogelaer JP. Primary prevention of glucocorticoid-induced osteoporosis with intravenous pamidronate and calcium: a prospective controlled 1-year study comparing a single infusion, an infusion given once every 3 months, and calcium alone. J Bone Miner Res 2001;16:104-12

80. Adachi JD, Bensen WG, Brown J, et al. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. N Engl J Med 1997;337:382-7

81. Cohen S, Levy RM, Keller M, et al. Risedronate therapy prevents

corticosteroid-induced bone loss: a twelve-month, multicenter, randomized,double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 1999;42:2309-18

82. Sambrook P, Birmingham J, Kelly P, et al. Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol, and calcitonin. N Engl J Med 1993;328:1747-52

83. Richy F, Ethgen O, Bruyere O, Reginster JY. Efficacy of alphacalcidol and calcitriol in primary and corticosteroid-induced osteoporosis: a meta-analysis of their effects on bone mineral density and fracture rate. Osteoporos Int 2004;15:301-10

84. Richy F, Schacht E, Bruyere O, et al. Vitamin D analogs vs native vitamin D in preventing bone loss and osteoporosis-related fractures: a comparative meta-analysis. Calcif Tissue Int 2005;76:176-86

85. Bernstein CN, Seeger LL, Anton PA, et al. A randomized, placebo-controlled trial of calcium supplementation for decreased bone density in corticosteroid-using patients with inflammatory bowel disease: a pilot study. Aliment Pharmacol Ther 1996;10:777-86

86. Buckley LM, Leib ES, Cartularo KS, et al. Calcium and vitamin D3 supplementation prevents bone loss in the spine secondary to low-dose corticosteroids in patients with rheumatoid arthritis—a randomized, doubleblind, placebo-controlled trial. Ann Intern Med 1996;125:961-8

87. Adachi JD, Bensen WG, Bianchi F, et al. Vitamin D and calcium in the prevention of corticosteroid-induced osteoporosis: a 3-year follow-up. J Rheumatol 1996;23:995-1000

88. Bijlsma JW, Raymakers JA, Mosch C, et al. Effect of oral calcium and vitamin D on glucocorticoid-induced osteopenia. Clin Exp Rheumatol 1988;6:113-19

89. Di Munno O, Beghe F, Favini P, et al. Prevention of glucocorticoid-induced osteopenia: effect of oral 25-hydroxyvitamin D and calcium. Clin Rheumatol 1989;8:202-7

90. Tałałaj M, Gradowska L, Marcinowska-Suchowierska E, et al. Efficiency of preventive treatment of glucocorticoid-induced osteoporosis with 25-hydroxyvitamin D3 and calcium in kidney transplant patients. Transplant Proc 1996;28:3485-7

91. Dykman TR, Haralson KM, Gluck OS, et al. Effect of oral 1,25-dihydroxyvitamin D and calcium on glucocorticoid-induced osteopenia in patients with rheumatic diseases. Arthritis Rheum 1984;27:1336-43

92. Sambrook P, Henderson NK, Keogh A, et al. Effect of calcitriol on bone loss after cardiac or lung transplantation. J Bone Miner Res 2000;15:1818-24

93. Ringe JD, Cöster A, Meng T, et al. Treatment of glucocorticoid-induced osteoporosis with alfacalcidol/calcium versus vitamin D/calcium. Calcif Tissue Int 1999;65:337-40

94. Homik J, Suarez-Almazor ME, Shea B, et al. Calcium and vitamin D for corticosteroid- induced osteoporosis. Cochrane Database Syst Rev 2000(2):CD000952

95. Amin S, LaValley MP, Simms RW, Felson DT. The role of vitamin D in corticosteroid-induced osteoporosis: a meta-analytic approach. Arthritis Rheum 1999;42:1740-51

96. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. N Engl J Med 1998;339:292-9

97. Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. N Engl J Med 2007;357:2028-39

98. Reid DM, Devogelaer JP, Saag K, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 2009;373:1253-63

•• **One year randomized comparative study that demonstrated superior prevention and treatment efficacy of ZOL compared to RIS in lumbar and hip BMD in GC-treated patients.**

99. Reid DM, Hughes RA, Laan RF, et al. Efficacy and safety of daily risedronate inthe treatment of corticosteroid induced osteoporosis in men andwomen:a randomized trial. European Corticosteroid Induced Osteoporosis Treatment Study. J Bone Miner Res 2000;15:1006-13

100. Reginster JY, Kuntz D, Verdickt W, et al. Prophylactic use of alfacalcidol in corticosteroid-induced osteoporosis. Osteoporosis Int 1999;9:75-81

101. De Nijs RN, Jacobs JW, Algra A, et al. Prevention and treatment of glucocorticoid-induced osteoporosis with active vitamin D3 analogues: a review with meta-analysis of randomized controlled trials including organ transplantation studies. Osteoporos Int 2004;15:589-602

102. De Nijs RN, Jacobs JW, Lems WF, et al. Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis. N Engl J Med 2006;355:675-84

103. Sambrook PN, Kotowicz M, Nash P, et al. Prevention and treatment of glucocorticoid-induced osteoporosis: a comparison of calcitriol, vitamin D plus calcium, and alendronate plus calcium. J Bone Miner Res 2003;18:919-24

104. Lips P. Relative value of 25(OH)D and 1,25(OH)2D measurements. J Bone Miner Res 2007;22:1668-71

105. Healey JH, Paget SA, Williams-Russo P, et al. A randomized controlled trial of salmon calcitonin to prevent bone loss in corticosteroid-treated temporal arteritis and polymyalgia rheumatica. Calcif Tissue Int 1996;58:73-80

106. Ringe JD, Welzel D. Salmon calcitonin in the therapy of corticoid-induced osteoporosis. Eur J Clin Pharmacol 1987;33:35-9

107. Tascioglu F, Colak O, Armagan O, et al. The treatment of osteoporosis in patients with rheumatoid arthritis receiving glucocorticoids: a comparison of alendronate and intranasal salmon calcitonin. Rheumatol Int 2005;26:21-9

108. Adachi JD, Bensen WG, Bell MJ, et al. Salmon calcitonin nasal spray in the prevention of corticosteroid-induced osteoporosis. Br J Rheumatol 1997;36:255-9

109. Kapetanakis EI, Antonopoulos AS, Antoniou TA, et al. Effect of long-term calcitonin administration on steroid-induced osteoporosis after cardiac transplantation. J Heart Lung Transplant 2005;24:526-32

110. Rizzato G, Tosi G, Schiraldi G, et al. Bone protection with salmon calcitonin (sCT) in the long-term steroid therapy of

chronic sarcoidosis. Sarcoidosis 1988;5:99-103

111. Montemurro L, Schiraldi G, Fraioli P, et al. Prevention of corticosteroid-induced osteoporosis with salmon calcitonin in sarcoid patients. Calcif Tissue Int 1991;49:71-6

112. Luengo M, Pons F, Martinez de Osaba MJ, Picado C. Prevention of further bone mass loss by nasal calcitonin in patients on long term glucocorticoid therapy for asthma: a two year follow up study. Thorax 1994;49:1099-102

113. Cranney A, Welch V, Adachi JD, et al. Calcitonin for the treatment and prevention of corticosteroid-induced osteoporosis. Cochrane Database Syst Rev 2000(2):CD001983

114. Plotkin L, Manolagas SC, Bellido T. Dissociation of the pro-apoptotic effects of bisphosphonates on osteoclasts from their anti-apoptotic effects on osteoblasts/osteocytes with novel analogs. Bone 2006;39:443-52

115. Roux C, Oriente P, Laan R, et al. Randomized trial of effect of cyclical etidronate in the prevention of corticosteroid-induced bone loss. Ciblos Study Group. J Clin Endocrinol Metab 1998;83:1128-33

116. Adachi JD, Saag KG, Delmas PD, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving GC: a randomized, double-blind, placebo-controlled extension trial. Arthritis Rheum 2001;44:202-11

117. Wallach S, Cohen S, Reid DM, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. Calcif Tissue Int 2000;67:277-85

- **Powered study demonstrating fracture risk reduction efficacy of RIS compared to placebo in GC-treated patients.**

118. Stoch SA, Saag KG, Greenwald M, et al. Once-weekly oral alendronate 70 mg in patients with glucocorticoid-induced bone loss: a 12-month randomized, placebo-controlled clinical trial. J Rheumatol 2009;36:1705-14

119. Ringe JD, Dorst A, Faber H, et al. Intermittent intravenous ibandronate injections reduce vertebral fracture risk in corticosteroid-induced osteoporosis: results from a long-term comparative study. Osteoporos Int 2003;14:801-7

120. Furukawa F, Kaminaka C, Ikeda T, et al. Preliminary study of etidronate for prevention of corticosteroid-induced osteoporosis caused by oral glucocorticoid therapy. Clin Exp Dermatol 2011;36:165-8

121. Sebaldt RJ, Ioannidis G, Adachi JD, et al. 36 month intermittent cyclical etidronate treatment in patients with established corticosteroid induced osteoporosis. J Rheumatol 1999;26:1545-9

122. Struys A, Snelder AA, Mulder H. Cyclical etidronate reverses bone loss of the spine and proximal femur in patients with established corticosteroid-induced osteoporosis. Am J Med 1995;99:235-42

123. Sebaldt RJ, Adachi JD, Bensen WG, et al. Intermittent cyclic therapy with etidronate prevents corticosteroid-induced bone loss: two years of follow-up. Scand J Rheumatol Suppl 1996;103:91-3

124. Mulder H, Struys A. Intermittent cyclical etidronate in the prevention of corticosteroid-induced bone loss. Br J Rheumatol 1994;33:348-50

125. Fujita T, Satomura A, Hidaka M, et al. Acute alteration in bone mineral density and biochemical markers for bone metabolism in nephrotic patients receiving high-dose glucocorticoid and one-cycle etidronate therapy. Calcif Tissue Int 2000;66:195-9

126. Loddenkemper K, Grauer A, Burmester GR, Buttgereit F. Calcium, vitamin D and etidronate for the prevention and treatment of corticosteroid-induced osteoporosis in patients with rheumatic diseases. Clin Exp Rheumatol 2003;21:19-26

127. Skingle SJ, Crisp AJ. Increased bone density in patients on steroids with etidronate. Lancet 1994;344:543-4

128. Jenkins EA, Walker-Bone KE, Wood A, et al. The prevention of corticosteroid-induced bone loss with intermittent cyclical etidronate. Scand J Rheumatol 1999;28:152-6

129. Geusens P, Dequeker J, Vanhoof J, et al. Cyclical etidronate increases bone density in the spine and hip of postmenopausal women receiving long term corticosteroid treatment. A double blind, randomised placebo controlled study. Ann Rheum Dis 1998;57:724-7

130. Pitt P, Li F, Todd P, et al. A double blind placebo controlled study to determine the effects of intermittent cyclical etidronate on bone mineral density in patients on long-term oral corticosteroid treatment. Thorax 1998;53:351-6

131. Cortet B, Hachulla E, Barton I, et al. Evaluation of the efficacy of etidronate therapy in preventing glucocorticoid-induced bone loss in patients with inflammatory rheumatic diseases. A randomized study. Rev Rhum Engl Ed 1999;66:214-19

132. Jinnouchi Y. Efficacy of intermittent etidronate therapy for corticosteroid-induced osteoporosis in patients with diffuse connective tissue disease. Kurume Med J 2000;47:219-24

133. Sato S, Takada T, Katsuki Y, et al. Longterm effect of intermittent cyclical etidronate therapy on corticosteroid-induced osteoporosis in Japanese patients with connective tissue disease: 7-year followup. J Rheumatol 2008;35:142-6

134. Campbell IA, Douglas JG, Francis RM, et al. Five year study of etidronate and/or calcium as prevention and treatment for osteoporosis and fractures in patients with asthma receiving long term oral and/or inhaled glucocorticoids. Thorax 2004;59:761-8

135. Sato S, Ohosone Y, Suwa A, et al. Effect of intermittent cyclical etidronate therapy on corticosteroid induced osteoporosis in Japanese patients with connective tissue disease: 3 year followup. J Rheumatol 2003;30:2673-9

136. Cauza E, Etemad M, Winkler F, et al. Pamidronate increases bone mineral density in women with postmenopausal or steroid-induced osteoporosis. J Clin Pharm Ther 2004;29:431-6

137. Kim SD, Cho BS. Pamidronate therapy for preventing steroid-induced osteoporosis in children with nephropathy. Nephron Clin Pract 2006;102(3-4):c81-7

138. Nzeusseu Toukap A, Depresseux G, Devogelaer JP, Houssiau FA. Oral pamidronate prevents high-dose glucocorticoid-induced lumbar spine bone loss in premenopausal connective tissue disease (mainly lupus) patients. Lupus 2005;14:517-20

139. Noguera A, Ros JB, Pavía C, et al. Bisphosphonates, a new treatment for glucocorticoid-induced osteoporosis in

children. J Pediatr Endocrinol Metab 2003;16:529-36

140. Reid IR, Schooler BA, Stewart AW. Prevention of glucocorticoid-induced osteoporosis. J Bone Miner Res 1990;5:619-23

141. Reid IR, King AR, Alexander CJ, Ibbertson HK. Prevention of steroid-induced osteoporosis with (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate (APD). Lancet 1988;1:143-6

142. Reid IR, Heap SW, King AR, Ibbertson HK. Two-year follow-up of bisphosphonate (APD) treatment in steroid osteoporosis. Lancet 1988;2:1144

143. Emkey R, Delmas PD, Goemaere S, et al. Changes in bone mineral density following discontinuation or continuation of alendronate therapy in glucocorticoid-treated patients: a retrospective, observational study. Arthritis Rheum 2003;48:1102-8

144. Okada Y, Nawata M, Nakayamada S, et al. Alendronate protects premenopausal women from bone loss and fracture associated with high-dose glucocorticoid therapy. J Rheumatol 2008;35:2249-54

145. Lems WF, Lodder MC, Lips P, et al. Positive effect of alendronate on bone mineral density and markers of bone turnover in patients with rheumatoid arthritis on chronic treatment with low-dose prednisone: a randomized, double-blind, placebo-controlled trial. Osteoporos Int 2006;17(5):716-23

146. Kaji H, Kuroki Y, Murakawa Y, et al. Effect of alendronate on bone metabolic indices and bone mineral density in patients treated with high-dose glucocorticoid: a prospective study. Osteoporos Int 2010;21:1565-71

147. Tee SI, Yosipovitch G, Chan YC, et al. Prevention of glucocorticoid-induced osteoporosis in immunobullous diseases with alendronate: a randomized, double-blind, placebo-controlled study. Arch Dermatol 2012;148:307-14

148. Reid DM, Adami S, Devogelaer JP, Chines AA. Risedronate increases bone density and reduces vertebral fracture risk within one year in men on corticosteroid therapy. Calcif Tissue Int 2001;69:242-7

149. Eastell R, Devogelaer JP, Peel NF, et al. Prevention of bone loss with risedronate in glucocorticoid-treated rheumatoid arthritis patients. Osteoporos Int 2000;11:331-7

150. Mok CC, Tong KH, To CH, et al. Risedronate for prevention of bone mineral density loss in patients receiving high-dose glucocorticoids: a randomized double-blind placebo-controlled trial. Osteoporos Int 2008;19:357-64

151. Thomas T, Horlait S, Ringe JD, et al. Oral bisphosphonates reduce the risk of clinical fractures in glucocorticoid-induced osteoporosis in clinical practice. Osteoporos Int 2013;24:263-9

152. Takei T, Itabashi M, Tsukada M, et al. Risedronate therapy for the prevention of steroid-induced osteoporosis in patients with minimal-change nephrotic syndrome. Intern Med 2010;49:2065-70

153. Kriel MH, Tobias JH, Creed TJ, et al. Use of risedronate to prevent bone loss following a single course of glucocorticoids: findings from a proof-of-concept study in inflammatory bowel disease. Osteoporos Int 2010;21:507-13

154. Katayama K, Matsuno T. Effects of bisphosphonates on fracture incidence and bone metabolism in rheumatoid arthritis patients in general practice taking long-term corticosteroid therapy: a retrospective study. Clin Drug Investig 2008;28:149-58

155. Lange U, Illgner U, Teichmann J, Schleenbecker H. Skeletal benefit after one year of risedronate therapy in patients with rheumatoid arthritis and glucocorticoid-induced osteoporosis: a prospective study. Int J Clin Pharmacol Res 2004;24:33-8

156. Roux C, Reid DM, Devogelaer JP, et al. Post hoc analysis of a single IV infusion of zoledronic acid versus daily oral risedronate on lumbar spine bone mineral density in different subgroups with glucocorticoid-induced osteoporosis. Osteoporos Int 2012;23:1083-90

157. Sambrook PN, Roux C, Devogelaer JP, et al. Bisphosphonates and glucocorticoid osteoporosis in men: results of a randomized controlled trial comparing zoledronic acid with Risedronate. Bone 2012;50:289-95

158. Devogelaer JP, Sambrook P, Reid DM, et al. Effect on bone turnover markers of once-yearl intravenous infusion of zoledronic acid versus daily oral risedronate in patients treated with glucocorticoids. Rheumatology 2013;52:1058-69

159. Ringe JD, Dorst A, Faber H, et al. Intermittent intravenous ibandronate injections reduce vertebral fracture risk in corticosteroid-induced osteoporosis: results from a long-term comparative study. Osteoporos Int 2003;14:801-7

160. Li EK, Zhu TY, Hung VY, et al. Ibandronate increases cortical bone density in patients with systemic lupus erythematosus on long-term glucocorticoid. Arthritis Res Ther 2010;12:R198

161. Hakala M, Kröger H, Valleala H, et al. Once-monthly oral ibandronate provides significant improvement in bone mineral density in postmenopausal women treated with glucocorticoids for inflammatory rheumatic diseases: a 12-month, randomized, double-blind, placebo-controlled trial. Scand J Rheumatol 2012;41:260-6

162. Fahrleitner-Pammer A, Piswanger-Soelkner JC, Pieber TR, et al. Ibandronate prevents bone loss and reduces vertebral fracture risk in male cardiac transplant patients: a randomized double-blind, placebo-controlled trial. J Bone Miner Res 2009;24:1335-44

163. Langdahl BL, Marin F, Shane E, et al. Teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: an analysis by gender and menopausal status. Osteoporos Int 2009;20:2095-104

164. Devogelaer JP, Adler RA, Recknor C, et al. Baseline glucocorticoid dose and bone mineral density response with teriparatide or alendronate therapy in patients with glucocorticoid-induced osteoporosis. J Rheumatol 2010;37:141-8

165. Saag KG, Zanchetta JR, Devogelaer JP, et al. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum 2009;60:3346-55

•• **36 month randomized comparative study that demonstrated superiority of TPDT compared to ALN in lumbar and hip BMD increase and vertebral fracture risk reduction in GC-treated patients.**

166. Eastell R, Chen P, Saag KG, et al. Bone formation markers in patients with glucocorticoid-induced osteoporosis

treated with teriparatide or alendronate. Bone 2010;46:929-34

167. Burshell AL, Möricke R, Correa-Rotter R, et al. Correlations between biochemical markers of bone turnover and bone density responses in patients with glucocorticoid-induced osteoporosis treated with teriparatide or alendronate. Bone 2010;46:935-9

168. Karras D, Stoykov I, Lems WF, et al. Effectiveness of teriparatide in postmenopausal women with osteoporosis and glucocorticoiduse: 3-year results from the EFOS study. J Rheumatol 2012;39:600-9

169. Glüer CC, Marin F, Ringe JD, et al. Comparative effects of teriparatide and risedronate in glucocorticoid-induced osteoporosis in men: 18-month results of the EuroGIOPs trial. J Bone Miner Res 2013;28:1355-68

170. Farahmand P, Marin F, Hawkins F, et al. Early changes in biochemical markers of bone formation during teriparatide therapy correlate with improvements in vertebral strength in men with glucocorticoid-induced osteoporosis. Osteoporos Int 2013;24:2971-81

171. Lane NE, Sanchez S, Modin GW, et al. Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. Results of a randomized controlled clinical trial. J Clin Invest 1998;102:1627-33

172. Sun P, Cai DH, Li QN, et al. Effects of alendronate and strontium ranelate on cancellous and cortical bone mass in glucocorticoid-treated adult rats. Calcif Tissue Int 2010;86:495-501

173. Hofbauer LC, Zeitz U, Schoppet M, et al. Prevention of glucocorticoid-induced bone loss in mice by inhibition of RANKL. Arthritis Rheum 2009;60:1427-37

175. Dore RK, Cohen SB, Lane NE, et al. Effects of denosumab on bone mineral density and bone turnover in patients with rheumatoid arthritis receiving concurrent glucocorticoids or bisphosphonates. Ann Rheum Dis 2010;69:872-5

Affiliation

Eustathios Kenanidis[1] MD PhD,
Michael E Potoupnis[1,2] MD PhD,
Panagiotis Kakoulidis[3] MD,
Andreas Leonidou[4] MD MSc MRCS,
Grigorios T Sakellariou[5] MD,
Fares E Sayegh[6] MD &
Eleftherios Tsiridis[†7] MD MSc PhD(Lond.) FRCS
[†]Author for correspondence
[1]Consultant Orthopaedic Surgeon, Aristotle University Medical School, Academic Orthopaedic Unit, Thessaloniki, Greece
[2]Aristotle University Medical School, Academic Orthopaedic Unit, Thessaloniki, Greece
[3]Resident in Orthopaedics, Aristotle University Medical School, Academic Orthopaedic Unit, Thessaloniki, Greece
[4]Senior Registrar in Orthopaedics, Aristotle University Medical School, Academic Orthopaedic Unit, Thessaloniki, Greece
[5]Associate Professor of Orthopaedic Surgery, Aristotle University Medical School, Academic Orthopaedic Unit, Thessaloniki, Greece
[6]Consultant Rheumatologist, Aristotle University Medical School, Academic Orthopaedic Unit, Thessaloniki, Greece
[7]Aristotle University Medical School, Academic Orthopaedic Unit, Thessaloniki, Greece
E-mail: etsiridis@doctors.org.uk