High incidence rate of vertebral fractures during chronic prednisone treatment, in spite of bisphosphonate or alfacalcidol use. Extension of the *Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis*-trial

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Abstract

Objective

In the 18 month "alendronate or alfacalcidol in glucocorticoid-induced osteoporosis"-trial (STOP-trial) patients with rheumatic diseases who started glucocorticoids were randomised to anti-osteoporosis therapy with either daily alendronate (10 mg) or alfacalcidol (1 μg). In the present observational open follow-up study of the STOP-trial, we report the long-term effects of risk factors on the incidence and pattern of vertebral fractures, assessed using the Genant method.

Results

Of the 201 included patients in the STOP-trial, 163 completed the trial and of those 116 underwent a follow-up radiography of the spine. Twenty-eight patients had developed one or more new vertebral fractures since the end of the STOP-trial. The majority of fractures was wedge shaped and the deformities were intermediate to severe in both the former alendronate and alfacalcidol group. Multiple logistic regression analysis showed that STOP-trial medication and presence of pre-existing fractures did not predict development of new fractures, whereas age and cumulative glucocorticoid-dose did.

Conclusion

During the follow-up 2.7 years after the STOP-trial both in the former alendronate and alfacalcidol group 24% of the patients underwent at least one new vertebral fracture. This underlines that prevention of vertebral fractures remains a clinical challenge, even when anti-osteoporosis drugs are prescribed.

Key words

Glucocorticoid induced osteoporosis, bisphosphonate, vitamin D, alendronate; alfacalcidol, rheumatic disease, vertebral fracture, STOP-trial

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Received on September 15, 2009; accepted in revised form on January 8, 2010.

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Competing interests: none declared.

Introduction

Rapidly after starting glucocorticoid (GC) therapy bone loss occurs (1), especially due to a reduction in number and function of osteoblasts leading to less bone formation on the one hand but also to an increase in osteoclast function and decreased intestinal calcium absorption, and renal calcium excretion, leading to increased bone resorption on the other hand (2-5). The consequence is osteoporosis, a disease which clearly has clinical relevance (6), also in male patients (7).Anti-osteoporosis therapy typically consists of calcium and vitamin D supplementation and bisphosphonates (8, 9). However, anabolic drugs, such as parathyroid hormone (PTH) and active vitamin D, increasing bone formation and improving micro-architecture (10-12), fit the pathogenesis of glucocorticoid-induced osteoporosis (GIOP) better than bisphosphonates. Indeed PTH has been shown to be more effective compared to alendronate to reduce vertebral fracture risk in GIOP (13). Furthermore, bisphosphonates have been associated with osteonecrosis of the jaw (14).

In the 18-month *alendronate or alfacalcidol in glucocorticoid-induced osteoporosis-trial* (STOP-trial), the active vitamin D metabolite alfacalcidol prevented glucocorticoid-induced bone loss in patients with rheumatic diseases starting GC therapy less effectively compared to alendronate (15). The primary outcome of the STOP-trial was bone mineral density (BMD) as a surrogate marker of fracture outcome(10). However, theoretically, active vitamin D could decrease the risk of osteoporotic fractures also by improving micro-architecture of bone and strength and coordination of muscles, reducing the risk of falling (16). These effects would not be assessable by measuring BMD. Although the STOP-trial had not been powered nor designed to detect differences in fractures, during both the trial and follow-up period the incidence and pattern of vertebral fractures has been accurately documented.

The primary aim of this study was to analyse the incidence, pattern and risk factors of vertebral fractures during and after the STOP-trial as a planned extension of the STOP-trial. The secondary aim of this study was to investigate whether base-line patient characteristics, risks factors and randomised STOP-trial medication were predictive of new vertebral fractures, to provide directions for the long-term use of anabolic and anti-resorptive treatment.

Materials and methods

Patients

Patients with an inflammatory rheumatic disease, in whom GCs were initiated (or had been started within the previous 12 weeks) in a daily dose of at least 7.5 mg prednisolone or equivalent for an expected period of 6 months or longer had been included in the STOP-trial, a multi-centre randomised, double-blind, double-placebo clinical trial of 18 months' duration. Approval for the trial and its follow-up had been given by the local Human Research Review Committees. The patients (n=201) had been randomised either for treatment with alendronate 10 mg and placebo-alfacalcidol daily or alfacalcidol 1 μg and placebo-alendronate daily. Participating centers, patient demographics and other study-details have been described elsewhere (15). At the end of the trial, blinding was removed and treatment of osteoporosis was left to the judgment of each physician. Radiograph assessment of the thoracic and lumbar spine was performed between 2 and 4 years after the trial; at that point treatment with glucocorticoids and anti-osteoporosis therapy were evaluated. This long-term evaluation had been pre-defined at the start of the STOP-trial.

Of the 201 patients included, 163 completed the STOP-trial, and 116 patients underwent a follow-up x-ray of the thoracic and lumbar spine. Eighty-eight patients filled out a questionnaire on previous GC use and anti-osteoporosis treatment during the follow-up visit.

Methods

For scoring of vertebral deformities, lateral radiographs of vertebrae T4 to L5 were evaluated qualitatively, semi-quantitatively and quantitatively. Only fractures of previously normal vertebral bodies were counted as new fractures. The anterior (a), medial (m), and

posterior (p) heights of each vertebra were measured. Because radiographs of the different centers had not been calibrated, absolute heights could not be calculated and heights ratios were used: the anterior/posterior ratio (a/p), medial/posterior ratio (m/p), and two posterior ratios (p/pu and p/pl). For the posterior ratios the posterior height of a given vertebra (p) was divided by the posterior height of the vertebra above (pu) to get the ratio p/pu and it was divided by the posterior height of the vertebra below (pl) to get the ratio p/pl. If one of the ratios (a/p, m/p, p/pu, p/pl) was ≤0.80, the vertebra was considered as wedge (a/p), biconcave (m/p), or crush (p/pu, p/pl) shaped deformed, respectively. Since this 20% threshold for definition of a fracture might be rather sensitive but less specific, semi-quantitative scoring was also applied using other thresholds: The shape and severity of deformed vertebrae were defined according to the proportions of ratios as described by Genant *et al*. (17). This method defines mild, intermediate and severe deformation using 20%, 25%, and 40% thresholds, respectively.

In addition, for every vertebra scored as deformed, a naked eye inspection was performed to try to distinguish between osteoporotic, degenerative, traumatic and other causes of the deformation. Two researchers (JH and HH) from different hospitals blindly and independent of each other analysed all x-rays. The level of agreement between the two researchers scoring at the 20% cut-off was 92% (standard error 0.045); differences in score classifications were resolved by discussion. If no consensus was achieved, the vertebra was excluded from analysis.

Statistical analyses

Differences between dichotomous data of patients with or without fractures were evaluated by Chi-square tests; differences between continuous data of these groups were evaluated by *t*-tests or Mann-Whitney-U tests, where appropriate. Multiple logistic regression analyses were used to study the effect of patient characteristics and risk factors (age, diagnosis, gender, allocated STOP-trial medication, pre-existing fractures, cumulative GC-dose, vitamin D level at baseline and anti-osteoporosis medication used after the STOP-trial) on the incidence of new vertebral fractures.

Table I. Characteristics of patients studied during follow-up*.

Vertebral x-ray taken during follow-up after STOP-trial - n.	**116 (100%)**
Duration of follow-up after STOP-trial - months	33±10
Age at follow-up after STOP-trial - years	65±12
Diagnosis - n.	
Rheumatoid arthritis	33 (37%)
Polymyalgia rheumatica	33 (37%)
Other, *e.g*. SLE, Myositis	30 (26%)
Female sex - n.	71 (61%)
Change in bone mineral density (BMD) during STOP-trial - percentage	
At lumbar spine	0.4±5.9
At femoral neck	-0.18±5.4
At total hip	0.07±4.8
Level of 25-OH-vitamin D at baseline - nmol/L	50±22
Vitamin D level <30nmol/L - n.	25 (22%)
Patients who used predniso(lo)ne during STOP-trial - n.	116 (100%)
Daily dose - mg	10.1±6.1
Cumulative dose - mg	6075±3596
Patients who used bisphosphonates during STOP-trial (e.g. alendronate) - n.	58 (50%)
Duration of bisphosphonate-use - months	18
Data in questionnaire filled out at follow-up after STOP-trial - n.	**88 (100%)**
Patients who used predniso(lo)ne during follow-up after STOP-trial - n.	59 (67%)
Daily dose - mg	7.5±6.08
Cumulative dose - mg	6439±6596
Patients who used bisphosphonates during follow-up after STOP-trial - n.	37 (42%)
Duration of bisphosphonate-use - months	28±9
Patients who used both predniso(lo)ne and bisphosphonates - n.	32 (36%)

*Plus-minus values are means ±SD.

Table II. Fracture characteristics of patients studied both during the STOP-trial and follow-up (n=116).

Number of patients with new fractures (n fractures)	
At baseline	8 (9)
During STOP-trial[1]	5 (9)
During follow-up[1]	28 (46)
Type of new fractures (n patients (n fractures))	
At baseline	
Wedge	7 (8)
Biconcave	1 (1)
Crush	–
During STOP-trial	
Wedge	5 (9)
Biconcave	–
Crush	–
During follow-up	
Wedge	16 (34)
Biconcave	3 (3)
Crush	9 (9)
Severity of new fractures (n patients (n fractures))[2]	
At baseline	
Mild (~20% - 25%)	1 (1)[3]
Intermediate (~25% - 40%)	7 (7)[3]
Severe (~40%)	1 (1)
During STOP-trial	
Mild (~20% - 25%)	–
Intermediate (~25% - 40%)	3 (7)
Severe (~40%)	2 (2)
During Follow-up	
Mild (~20% - 25%)	12 (19)
Intermediate (~25% - 40%)	12 (23)
Severe (~40%)	4 (4)

Only patient characteristics of patients studied during both the STOP-trial and follow-up thereafter are shown here; therefore the data are different from the STOP-trial data (15). No statistical differences were found between former treatment groups (Alendronate *vs*. alfacalcidol).
[1]During the STOP-trial: between 0 and 18 months; During follow-up: between 18 and 50.7 months.
[2]Definition of fracture severity according to the Genant method (17).
[3]One patient had both an intermediate and a mild fracture.

Results

In 116 patients a follow-up x-ray of the vertebral spine was taken on average 2.7 (standard deviation (SD) 0.8) years after the blinded STOP-trial. Withdraw-

al reasons of the other patients were (1) non-response to the invitation, (2) death, (3) unwillingness to participate. The 116 patients who were studied during follow-up did not differ in demographic (age, diagnosis, or gender) or study characteristics (change in BMD and serum vitamin D levels) compared to the 201 patients who were included in the STOP-trial, or compared to the group withdrawn during the STOP-trial nor the group lost to follow-up (data not shown). This suggests that the results of this study are generalisable to the whole trial population. Patients who used GCs during follow-up only used predniso(lo)ne as preparations and almost all used alendronate as bisphosphonate.

In 28 patients, one or more new vertebral fractures since the end of the trial were seen. On the naked eye inspection, all fractures were deemed to be osteoporotic, except for one probable malignant fracture; this patient has not been included in the analyses. Most fractures were located at thoracic vertebra 9 to lumbar vertebra 1; the location of fractures did not differ between the two former allocated treatment groups (data not shown). Many patients developed multiple, mostly wedge-type, and mostly intermediate type-type vertebral fractures during the STOP-trial and follow-up period (Table II). Table III shows characteristics of patients who had developed a vertebral fracture during follow-up, compared to data of patients who had not. Multiple logistic regression analyses (independent variables: age, diagnosis, gender, STOP-trial medication, pre-existing fractures, cumulative GC-dose, vitamin D level at baseline and anti-osteoporosis medication used after the STOP-trial), showed that allocated STOP-trial medication, and pre-existing fractures did not predict new vertebral fractures (dependent variable), whereas age and cumulative GC-dose did (Table IV).

Table III. Characteristics of patients with and without new fractures at follow-up (n=116)*.

	New fractures during follow-up (28 patients; 46 fractures)	No new fractures during follow-up (88 patients)
Vertebral X-ray taken during follow-up after STOP-trial - n.	**28 (100%)**	**88 (100%)**
Duration of follow-up after STOP-trial - months	32 ±10	33±10
Age at follow-up after STOP-trial - years	70 ±9	63±12
Diagnosis - n.		
Rheumatoid arthritis	9 (32%)	34 (39%)
Polymyalgia rheumatica	11 (39%)	32 (36%)
Other, *e.g.* SLE, Myositis	8 (29%)	22 (25%)
Female sex - n.	17 (61%)	54 (61%)
Change in bone mineral density (BMD) during the STOP-trial - percentage		
At lumbar spine	0.7 ±4.5	0.3±6.4
At femoral neck	-1.3 ±5.4	0.2±5.3
At total hip	-0.5 ±4.6	0.3±4.9
Level of 25-OH-vitamin D at baseline - nmol/L	47 ±26	51±21
Vitamin D level <30nmol/L - n.	10 (36%)	15 (17%)
Patients with fractures at baseline - n.	2 (7%)	6 (7%)
Total fractures at baseline - n.	2	7
Patients with new fractures during the STOP-trial - n.	1 (4)	4 (5)
Total fractures during the STOP-trial — n.	2	7
Patients who used predniso(lo)ne during the STOP-trial - n.	28 (100%)	88 (100%)
Mean daily predniso(lo)ne-dose - mg	9.8 ±4.5	10.2±6.6
Cumulative predniso(lo)ne-dose - mg	6024 ±2724	6091±3846
Patients who used bisphosphonates during the STOP-trial (*i.e.* alendronate group) - n.	14 (50%)	44 (50%)
Duration of bisphosphonate-use - months	18	18
Questionnaire filled in during follow-up after STOP-trial — no.	**20 (100%)**	**68 (100%)**
Patients who used predniso(lo)ne during follow-up after the STOP-trial - n.	16 (80%)	43 (63%)
Mean daily predniso(lo)ne-dose - mg	6.0 ±3.5	7.3±5.1
Cumulative predniso(lo)ne-dose - mg	5336 ±4551	5783±4993
Patients who used bisphosphonates during follow-up after the STOP-trial - n.	10 (50%)	27 (40%)
Duration of bisphosphonate-use - months	28 ±12	26±8
Patients who used both predniso(lo)ne and bisphosphonates during follow-up after the STOP-trial - n.	10 (50%)	22 (32%)

*Plus-minus values are means ±SD. There were no significant differences between the two groups.

Discussion

Over 4 years, after the start of the STOP-trial, a considerable proportion of the patients, *i.e.* 28%, had new morphometric vertebral fractures. The majority of these deformities was intermediate to severe, and located at the lower thoracic/upper lumbar vertebrae. The high incidence of radiological vertebral fractures has significant clinical relevance, since they increase limited-activity days and bed-disability (18), and are a risk factor for new vertebral and hip fractures (19). The severity of vertebral deformations could indicate that our population had ongoing deterioration of bone micro-architecture.

Although the incidence of vertebral fractures during the STOP-trial period did not differ from that reported in other trials on anti-osteoporotic treatment (20), our study is the first analysing the pattern of vertebral fracturing at the start, during and after randomised treatment of GIOP with an anti-resorptive compared to an anabolic agent. Similar to studies in rheumatoid arthritis (RA) patients treated with GCs (21, 22), the number of vertebral fractures may have been influenced by disease activity of the included patients, since inflammatory diseases like RA are known for their harmful effects on bone (23, 24).

Age and cumulative GC-dose of the patients were predictors of new vertebral fractures. This finding reflects the well known pathology of glucocorticoid induced bone loss, and both risk factors have been widely included in guidelines on GIOP (25). Our study further underlines the vulnerability for osteoporosis of elderly who use long-term GCs.

Table IV. Multiple logistic regression analysis of prognostic factors for new vertebral fractures (≥1) during follow-up.

Patient characteristic	Odds ratio	95% Confidence interval	Coefficient (beta)	Standard error
Age	1.14	1.05;1.23	0.13	0.04
Cumulative GC-dose (in mg) during both STOP-trial and follow-up	1.00016	1.00003;1.00029	0.00016	0.00007
Diagnosis (PMR, RA, or other)	1.41	0.31;6.40	0.34	0.77
Sex	1.96	0.47;7.98	0.67	0.72
STOP-trial treatment (alendronate vs. alfacalcidol)	1.90	0.51;7.07	0.64	0.67
Pre-existent fractures	0.38	0.04;3.30	-0.97	1.11
Bisphosphonate use after STOP-trial	0.52	0.11;2.49	-0.65	0.80
Calcium and vitamin D use after STOP-trial	0.49	0.08;3.00	-0.71	0.92
Baseline level of 25OH-vitamin D	0.99	0.96;1.03	-0.0075	0.016

The early effects of alendronate on BMD after 18 months were not reflected in a significantly decreased vertebral fracture rate at follow-up. However, the 18 month STOP-trial had been designed to study BMD as primary outcome and possibly the follow-up was underpowered to study the long-term effects (*i.e.* vertebral fractures) because of the substantial withdrawal that was encountered during this period.

We did not include change in BMD during the STOP-trial as independent variable in the logistic regression for two reasons. First, because alendronate acts via increase of BMD and alfacalcidol also via other mechanisms, this would have had an unbalanced influence on the included independent variable allocated STOP-trial medication. Second, patients of both former treatment groups were roughly equally treated for GIOP during follow-up after the STOP-trial, which could mean there was a 'catch-up' effect in BMD in the former alfacalcidol group, diluting the differences in BMD between the two former groups.

A possible role of vitamin D throughout the trial and follow-up thereafter cannot be ignored. Although not significantly, the prevalence of hypovitaminosis D at baseline was twice as high in patients who suffered from fractures during follow-up (Table III) compared to that of those who did not. Although supplemented adequately during the trial, the bone in these former patients could nevertheless have suffered from residual effects of osteomalacia. Furthermore, it should be noted that patients had a higher risk of developing hypovitaminosis D during the follow-up period after the trial due to the frequent switch from alfacalcidol to bisphosphonate therapy and to the stopping of the vitamin D supplementation (given during the trial per protocol in case of hypovitaminosis D at baseline).

An important result of our study is that 1 out of 3 to 4 patients treated with GCs develops vertebral fractures within approximately 4 years. This high incidence of fractures is mainly related to GCs, disease activity and age, as described above. Although the physicians participating in our study were all member of the Osteoporosis Working Group of the Dutch Society for Rheumatology, and thus osteoporosis-minded, there might have been suboptimal treatment of GIOP during the follow-up after the STOP-trial. In the Netherlands, national guidelines for treating GIOP only got published in 2004 (25), advising more uniform and intensive treatment strategies than those probably applied during follow-up. Furthermore, patient compliance is known to be often suboptimal (26). In order to achieve a better long-term effect it is necessary to maintain intensive treatment. Specific attention with regards to anti-osteoporosis treatment should be paid to GC-using patients of older age and/or with a high cumulative GC-dose.

Future research should focus on combination strategies to prevent GIOP, *e.g.* with active vitamin D added to anti-osteoporosis regimes with an anti-resorptive drug or *sequential* therapy with PTH and bisphosphonates, as *concomitant* therapy with PTH and bisphosphonate was not beneficial in postmenopausal women (27). PTH was more effective than alendronate in preventing morphometric vertebral fractures in GIOP (13), but duration of this treatment is limited. An additional important item for future studies and clinical practice is how to increase adherence to treatment and treatment guidelines in patients and physicians, respectively. The latter should particularly focus on high-risk patients such as high cumulative dose GC-users and older patients, as our study has confirmed their precarious position.

In conclusion, our study indicates that during current treatment strategies for GIOP vertebral fractures still occur on a large scale, with age and cumulative GC-use as important predictors of new vertebral fractures.

Key messages

1) During the follow-up 2.7 years after the *Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis*-trial (STOP-trial), in 24% of the patients at least one new vertebral fracture occurred.

2) Prevention of vertebral fractures remains a clinical challenge, even when anti-osteoporosis drugs are prescribed.

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