Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study

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Summary

Background Glucocorticoid-induced osteoporosis is the most common form of secondary osteoporosis and is associated with an estimated annual fracture rate of 5%. We aimed to assess the efficacy and safety of denosumab compared with risedronate in glucocorticoid-induced osteoporosis.

Methods We did a 24-month, double-blind, active-controlled, double-dummy, non-inferiority study at 79 centres in Europe, Latin America, Asia, and North America. Eligible patients were aged 18 years or older and were receiving glucocorticoids (≥7·5 mg prednisone daily, or equivalent) for at least 3 months (glucocorticoid continuing) or less than 3 months (glucocorticoid initiating) before screening. Patients younger than 50 years needed to have a history of osteoporosis-related fracture; glucocorticoid-continuing patients aged 50 years or older needed a lumbar spine, total hip, or femoral neck bone mineral density T score of –2·0 or less, or –1·0 or less if they had a history of osteoporosis-related fracture. Participants were randomly assigned (1:1) to either 60 mg subcutaneous denosumab every 6 months and oral placebo daily for 24 months, or 5 mg oral risedronate daily and subcutaneous placebo every 6 months for 24 months. Randomisation was stratified by sex within each subpopulation, and was done with an interactive voice-response system. Active drugs and corresponding placebos had identical packaging, labels, and appearance. The primary outcome was non-inferiority of denosumab to risedronate in terms of percentage change from baseline in lumbar spine bone mineral density at 12 months based on non-inferiority margins (–0·7 and –1·1 percentage points for the glucocorticoid-continuing and glucocorticoid-initiating subpopulations, respectively). Superiority was also assessed as a secondary outcome. The primary efficacy set included all randomly assigned participants who had a baseline and postbaseline lumbar spine bone mineral density measurement, and was analysed according to randomised treatment assignment. The safety analysis set included all randomly assigned participants who received at least one dose of investigational product, and was analysed by actual treatment received. This study is registered with ClinicalTrials.gov (NCT01575873) and is completed.

Findings Between March 28, 2012, and June 30, 2015, 795 patients, 505 of whom were glucocorticoid continuing and 290 of whom were glucocorticoid initiating, were enrolled and randomly assigned (398 to denosumab, 397 to risedronate). Denosumab was both non-inferior and superior to risedronate at 12 months for effect on bone mineral density at the lumbar spine in both glucocorticoid-continuing (4·4% [95% CI 3·8–5·0] *vs* 2·3% [1·7–2·9]; p<0·0001) and glucocorticoid-initiating (3·8% [3·1–4·5] *vs* 0·8% [0·2–1·5]; p<0·0001) subpopulations. Incidence of adverse events, serious adverse events (including infections), and fractures was similar between treatment groups. The most common adverse events were back pain (17 [4%] patients in the risedronate group and 18 [5%] in the denosumab group) and arthralgia (21 [5%] patients in the risedronate group and 17 [4%] in the denosumab group). Serious infection occurred in 15 (4%) patients in the risedronate group and 17 (4%) patients in the denosumab group.

Interpretation Denosumab could be a useful treatment option for patients newly initiating or continuing glucocorticoids who are at risk of fractures.

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Introduction

Despite advances in targeted therapies for many immune-mediated diseases, glucocorticoids are still used long term by an estimated 1% of the population.[1] Glucocorticoid-induced osteoporosis is the most common form of secondary osteoporosis[2] and is associated with an estimated annual fracture rate of 5%.[3] Fracture risk in glucocorticoid users is related to dose and duration of glucocorticoid use,[3–5] and the underlying disease necessitating glucocorticoid therapy.[5] The pathophysiology of glucocorticoid-induced osteoporosis is mediated via accelerated bone resorption, particularly in the early phase, and a reduction in bone formation. Therefore, both antiresorptive and anabolic drugs have been investigated, with small but significant increases in bone mineral density noted in the spine and, to a lesser extent, the hip.[6–9]

RANKL has an important role in the pathogenesis of glucocorticoid-induced osteoporosis. Its production

Research in context

Evidence before this study

Glucocorticoid-induced osteoporosis is the most common form of secondary osteoporosis, and increases the risk of vertebral and non-vertebral fractures. However, treatment rates are low, despite the availability of therapies. We searched PubMed with the terms "glucocorticoid-induced osteoporosis" and "denosumab", "risedronate", "bisphosphonate", "teriparatide", or "PTH analog" for articles published in any language in peer-reviewed journals up to Nov 7, 2017. We reviewed all publications in which the results of randomised clinical trials were reported. Randomised controlled trials have been done to assess several therapies for glucocorticoid-induced osteoporosis, including alendronate, risedronate, zoledronic acid, and teriparatide. The results of these trials suggest that these drugs efficaciously maintain or increase bone mass.

Added value of this study

To our knowledge, ours is the first large, randomised controlled trial of denosumab in patients with glucocorticoid-induced osteoporosis who were either prevalent glucocorticoid users or newly initiating glucocorticoid therapy. The 12-month results of this 24-month study showed that denosumab was superior to risedronate, a commonly used bisphosphonate for glucocorticoid-induced osteoporosis, in increasing bone mineral density at the lumbar spine. The two treatment groups had similar safety profiles.

Implications of all the available evidence

Our findings suggest that denosumab is efficacious and well tolerated as a treatment option in glucocorticoid-induced osteoporosis.

is increased by glucocorticoid use, which results in overwhelming of the natural decoy receptor osteoprotegerin, leading to accelerated bone resorption.[10] Denosumab is a fully human monoclonal antibody that binds and neutralises the activity of human RANKL, similar to the action of endogenous osteoprotegerin. Denosumab inhibited cortical bone loss without impairing biomechanical strength in a murine model of glucocorticoid-induced osteoporosis.[11] In a phase 2 trial[12] in patients with rheumatoid arthritis who were taking glucocorticoids, 60 or 180 mg of denosumab every 6 months was associated with significant gains in bone mineral density at 12 months compared with placebo. Denosumab also increases bone density and reduces vertebral, non-vertebral, and hip fracture risk in postmenopausal women with osteoporosis.[13] This pathophysiological and clinical evidence, coupled with low adherence to treatment and prevention strategies for glucocorticoid-induced osteoporosis in long-term users of glucocorticoids,[14,15] provided the rationale for this study of denosumab compared with risedronate, which is an efficacious treatment for glucocorticoid-induced osteoporosis,[7,16] in patients who are either beginning or on sustained glucocorticoid therapy.

Methods

Study design and participants

We did a phase 3, international, randomised, double-blind, double-dummy, active-controlled, non-inferiority study at 79 primary care and specialist centres in 16 countries in Europe, Latin America, Asia, and North America (appendix). Eligible participants were aged 18 years or older and were taking glucocorticoids (≥7·5 mg prednisone, or its equivalent daily). Participants who had been taking glucocorticoids for at least 3 months were classed as glucocorticoid continuing; those who were taking glucocorticoids for less than 3 months were classed as glucocorticoid initiating. Patients younger than 50 years had to have a history of osteoporosis-related fracture. Glucocorticoid-continuing patients aged 50 years or older were required to have a lumbar spine, total hip, or femoral neck bone mineral density T score of –2·0 or less, or a T score of –1·0 or less with a history of osteoporosis-related fracture. The full list of inclusion and exclusion criteria are detailed in the appendix.

See Online for appendix

This study was done in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The trial protocol was reviewed and approved by independent ethics committees or institutional review boards at each study centre. All patients provided written informed consent.

Randomisation and masking

Investigators at study sites enrolled patients. After completing all screening procedures and meeting all eligibility criteria, the investigator called an interactive voice response system for a randomisation assignment. Eligible patients were randomly assigned (1:1) to 60 mg subcutaneous denosumab every 6 months and oral placebo given daily for 24 months, or 5 mg oral risedronate daily and subcutaneous placebo every 6 months for 24 months within each subpopulation (appendix). Randomisation was stratified by sex within each subpopulation, and was prepared by the funder's Global Randomization and Blinding group independent of the study team before study initiation. Investigators, study centre, patients, and people analysing the data were blinded to the study treatment. Masking was achieved by ensuring that the active drugs and corresponding placebos had identical packaging, labels, and appearance. Enrolment of men was restricted to 30–40% to ensure balance in view of the possible differing magnitude of bone mineral density increases between the sexes (because enrolment of men

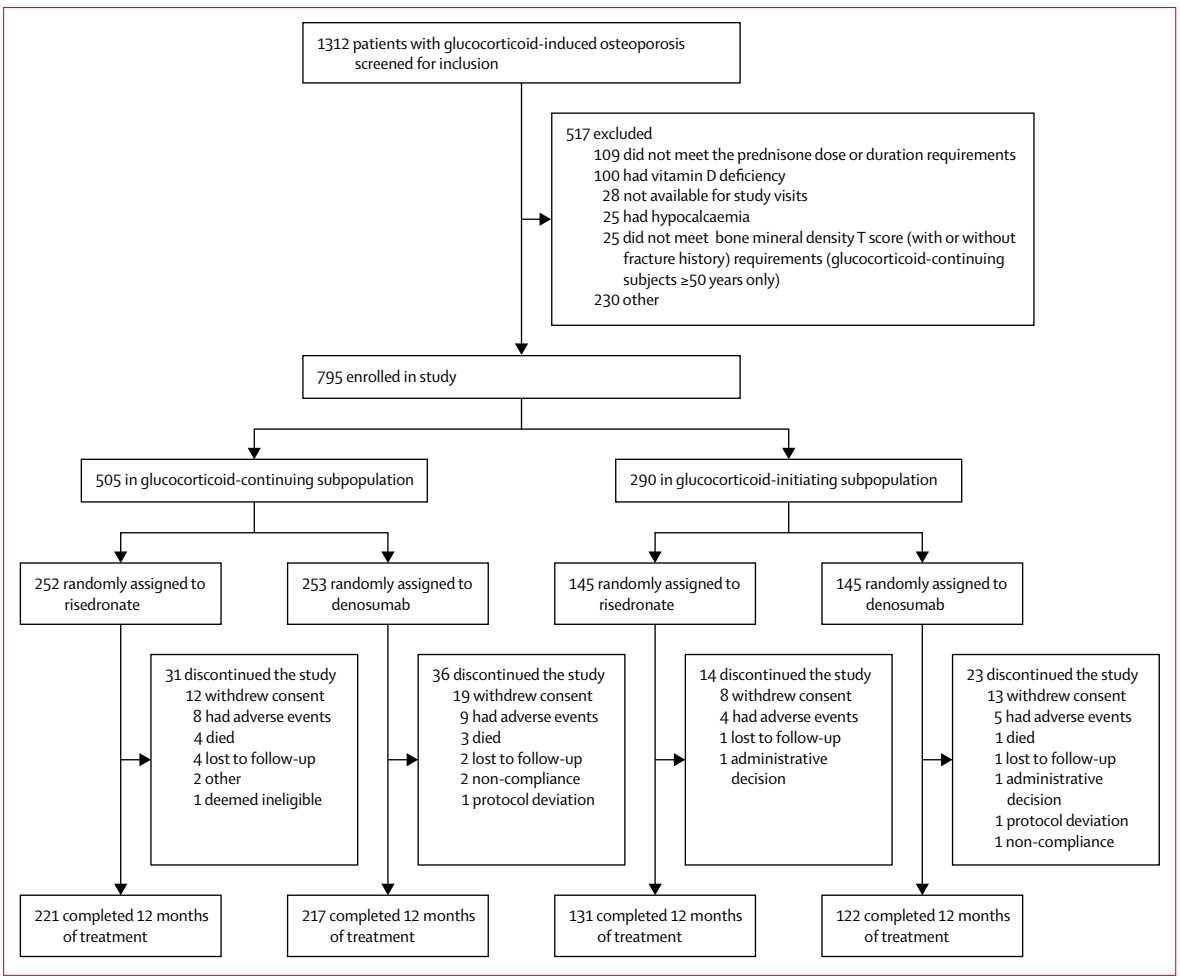

Figure 1: **Trial profile**

was always below 40%, no proactive steps needed to be taken).

Procedures

In addition to study treatment, all patients took at least 1000 mg calcium and at least 800 IU vitamin D daily for the duration of the study. Adherence to oral therapy was assessed with returned pill counts at each post-baseline visit. Patients' primary or specialist physicians managed their glucocorticoid therapy. All patients were assessed 10 days, 6 months, and 12 months after baseline. Bone mineral density was measured by dual-energy x-ray absorptiometry (Lunar [Madison, WI, USA] or Hologic [Waltham, MA, USA]) at the lumbar spine (at screening, 6 months, and 12 months) and hip (at screening and 12 months), and was centrally analysed (BioClinica, Newark, CA, USA).

Patients at selected sites were also given the opportunity to participate in a prespecified bone turnover marker substudy, in which serum was collected to assess concentrations of markers of bone resorption (ie, CTX) and formation (ie, P1NP). Concentrations were measured at baseline, on day 10, and at 3, 4, 5, 6, and 12 months. CTX was assessed centrally by Esoterix Laboratory Services (Calabasas, CA, USA) with IDS-iSYS (Immunodiagnostic Systems Holdings, Tyne & Wear, UK) based on chemiluminescence technology. P1NP was analysed centrally by Covance Central Laboratory Services (Indianapolis, IN, USA) with UniQ P1NP radioimmunoassay.

A central facility (BioClinica, Newark, CA, USA) provided the Genant semi-quantitative grading[17] of lateral thoracic and lumbar spine radiographs, which were taken on day 1 and at 12 months (or at early termination) to identify prevalent and incident vertebral fractures, or at unscheduled visits for clinical vertebral fractures. Non-vertebral fractures were recorded via adverse event reporting.

Participants were asked about adverse events and concomitant medications at each study visit. Potential cases of osteonecrosis of the jaw and atypical femoral fracture, which were identified on the basis of prespecified search criteria, were reviewed by independent, masked,

external adjudication committees, who used published case definitions.[18,19]

Outcomes

The prespecified primary analysis occurred after patients had the opportunity to complete the 12-month study visit, but patients continued masked treatment for a further 12 months; the 24-month efficacy and safety results will be reported separately. The primary outcome was non-inferiority of denosumab to risedronate with respect to percentage change from baseline in lumbar spine bone mineral density at 12 months in the glucocorticoid-continuing and glucocorticoid-initiating subpopulations separately. The secondary efficacy outcomes assessed at 12 months were superiority of denosumab over risedronate in terms of percentage change from baseline in lumbar spine and total hip bone mineral density in both subpopulations separately.

Exploratory outcomes reported here were percentage change from baseline in femoral neck bone mineral density at 12 months and lumbar spine bone mineral density at 6 months in both subpopulations separately, and bone turnover markers (CTX and P1NP) in the combined population. Other exploratory outcomes that were assessed but are not reported here were bone mineral density at the trochanter and 1/3 radius, high-resolution peripheral quantitative CT of the radius and tibia, treatment preference and satisfaction with 6-monthly injections versus daily oral tablets, bone histology and histomorphometry at 12 and 24 months, and bone turnover markers and femoral neck bone mineral density at 24 months.

For safety assessment, we compared denosumab with risedronate in the combined subpopulations for incidence of adverse events, serious adverse events, laboratory abnormalities, and anti-denosumab antibodies.

	Glucocorticoid continuing		Glucocorticoid initiating	
	Risedronate (N=252)	Denosumab (N=253)	Risedronate (N=145)	Denosumab (N=145)
Sex				
Male	67 (27%)	68 (27%)	52 (36%)	52 (36%)
Female	185 (73%)	185 (73%)	93 (64%)	93 (64%)
Premenopausal	25 (14%)	24 (13%)	7 (8%)	10 (11%)
Postmenopausal	157 (85%)	159 (86%)	83 (89%)	82 (88%)
Unknown	3 (2%)	2 (1%)	3 (3%)	1 (1%)
Ethnic origin				
White	223 (88%)	230 (91%)	123 (85%)	122 (84%)
Asian	12 (5%)	6 (2%)	9 (6%)	9 (6%)
Black or African American	4 (2%)	4 (2%)	2 (1%)	2 (1%)
Other	13 (5%)	13 (5%)	11 (8%)	12 (8%)
Age, years	61·3 (11·1)	61·5 (11·6)	64·4 (10·0)	67·5 (10·1)
Medical conditions necessitating glucocorticoid therapy*				
Rheumatological disorders	184 (73%)	173 (68%)	129 (89%)	129 (89%)
Rheumatoid arthritis	119 (47%)	96 (38%)	46 (32%)	49 (34%)
Polymyalgia rheumatica	18 (7%)	21 (8%)	52 (36%)	51 (35%)
Systemic lupus erythematosus	16 (6%)	15 (6%)	4 (3%)	2 (1%)
Vasculitis	9 (4%)	15 (6%)	10 (7%)	7 (5%)
Other	30 (12%)	38 (15%)	34 (23%)	32 (22%)
Respiratory disorders	37 (15%)	46 (18%)	11 (8%)	12 (8%)
Chronic obstructive pulmonary disease	5 (2%)	7 (3%)	1 (1%)	1 (1%)
Asthma	17 (7%)	20 (8%)	2 (1%)	3 (2%)
Other	16 (6%)	20 (8%)	8 (6%)	8 (6%)
Inflammatory bowel disease	5 (2%)	3 (1%)	0 (0%)	1 (1%)
Sarcoidosis	5 (2%)	4 (2%)	0 (0%)	0 (0%)
Neurological disorders	15 (6%)	11 (4%)	2 (1%)	1 (1%)
Dermatological disorders	8 (3%)	9 (4%)	5 (3%)	6 (4%)
Other	37 (15%)	46 (18%)	11 (8%)	12 (8%)
Daily prednisone-equivalent dose, mg				
Mean (SD)	11·1 (7·7)	12·3 (8·1)	15·6 (10·3)	16·6 (13·0)
Median (IQR)	10·0 (7·5–10·0)	10·0 (7·5–12·5)	12·5 (9·0–20·0)	12·5 (10·0–20·0)
Duration of previous oral glucocorticoid use†				
0 to <3 months	8 (3%)	13 (5%)	129 (89%)	133 (92%)
≥3 months	242 (96%)	239 (94%)	16 (11%)	10 (7%)
3 to <12 months	75 (30%)	81 (32%)	8 (6%)	7 (5%)
≥12 months	167 (66%)	158 (62%)	8 (6%)	3 (2%)
Missing or daily dose <7·5 mg	2 (1%)	1 (<1%)	0 (0%)	2 (1%)

(Table 1 continues on next page)

Statistical analysis

All efficacy endpoints were analysed according to original randomised treatment assignments. Analyses of month 12 primary and secondary efficacy endpoints and testing procedures were performed independently within the glucocorticoid-continuing and glucocorticoid-initiating subpopulations. We used a fixed sequence for statistical testing: the primary efficacy endpoint—lumbar spine bone mineral density (non-inferiority)—was assessed first, followed by the secondary efficacy endpoint of lumbar spine bone mineral density (superiority), and then the secondary efficacy endpoint of total hip bone mineral density (superiority). Formal inferential testing could proceed to the next step only when significance was declared in the current step.

Primary and secondary efficacy endpoints were analysed with an ANCOVA model, with main effects for treatment, sex, baseline bone mineral density, and machine type, and an interaction effect for baseline bone mineral density and machine type. For the glucocorticoid-continuing subpopulation, duration of previous glucocorticoid use (<12 months *vs* ≥12 months) was an additional covariate in the model. Because missing bone mineral density values were not imputed, only patients with bone mineral density data at baseline and at 12 months were included in the primary efficacy analysis. Diagnostic plots were generated to examine model assumptions. The residuals were normally distributed, and the variance of the residuals seemed constant over the range of predicted values without apparent outliers. Least-squares mean point estimates of

the percentage change from baseline were determined for each treatment group. Two-sided 95% CIs and associated p values were calculated for the difference between the least-squares means (denosumab minus risedronate). For the non-inferiority test within each subpopulation of the primary endpoint, a two-sided 95% CI for the treatment contrast was constructed, and its lower bound was compared with the prespecified non-inferiority margins (–0·7 and –1·1 percentage points for the glucocorticoid-continuing and glucocorticoid-initiating subpopulations, respectively), which were chosen on the basis of the results of two placebo-controlled studies, one of risedronate in patients with glucocorticoid-induced osteoporosis, the other of zoledronic acid in a similar population, in which risedronate was the active comparator.[6,7,16]

We calculated that a sample size of 496 patients in the glucocorticoid-continuing subpopulation and 280 patients in the glucocorticoid-initiating subpopulation would achieve a statistical power greater than 99% in each subpopulation to reject a null hypothesis of inferiority, assuming that the expected differences in means were 1·06 and 1·56 percentage points for glucocorticoid-continuing and glucocorticoid-initiating subpopulations, respectively, with a one-sided two-sample *t* test and a significance level of 0·025. A dropout rate of 15% during the first 12 months of the study was assumed in the sample size calculation for the primary endpoint. Based on the planned sample size and dropout rate, the statistical power for the secondary (superiority) endpoint was 90% or greater in each subpopulation to detect a significantly greater difference in percentage change in bone mineral density at the lumbar spine and total hip between the treatment groups at 12 months.

A sensitivity analysis for the primary endpoint was done in a subset of patients who did not have important protocol deviations and met the minimum exposure to the treatments (per-protocol analysis)—ie, they received both planned denosumab doses (or matching placebo) and at least 80% of the planned risedronate doses (or matching placebo) in the 12 months of treatment. Post-hoc sensitivity analyses for missing data for percentage change from baseline in bone mineral density were done in each subpopulation—specifically, a repeated measures model without imputation, an ANCOVA model with baseline-value-carried-forward imputation, and an ANCOVA model with multiple imputation.

We used non-parametric methods to analyse percentage changes from baseline for bone turnover markers in the combined subpopulations. A Wilcoxon rank sum test was used to compare treatment groups. Analyses included patients in the bone turnover marker substudy who had recorded data at timepoints of interest. Undetectable values were imputed with the corresponding assay's established lower limit of detection value.

Safety analyses included patients who received at least one dose of risedronate or denosumab. Safety endpoints were summarised according to the actual treatment received for the combined subpopulations with the Medical Dictionary for Regulatory Activities (version 19.0). Serious infections were also assessed in subgroups of patients receiving concomitant biologics or any (biologic or non-biologic) immunosuppressants.

Osteoporosis-related fractures, comprising new and worsening vertebral fractures and low-trauma non-vertebral fractures, were summarised descriptively for patient incidence and event incidence for the combined subpopulations. New and worsening vertebral fractures were assessed in patients who had a baseline and at least one post-baseline spine radiograph taken. Low-trauma non-vertebral fractures were assessed in patients who received at least one dose of risedronate or denosumab. Fractures associated with high trauma severity, pathological fractures, or fractures of the skull, facial bones, metacarpals, fingers, and toes were excluded from the fracture summary.

All statistical analyses were done in SAS (version 9.4). The study is registered with ClinicalTrials.gov, number NCT01575873.

	Glucocorticoid continuing		Glucocorticoid initiating	
	Risedronate (N=252)	Denosumab (N=253)	Risedronate (N=145)	Denosumab (N=145)
(Continued from previous page)				
Baseline immunosuppressant use				
Biologic or non-biologic immunosuppressants	135 (54%)	122 (48%)	51 (35%)	52 (36%)
Biologics	12 (5%)	7 (3%)	6 (4%)	5 (3%)
Non-biologics	133 (53%)	120 (47%)	48 (33%)	50 (34%)
25-hydroxyvitamin D, ng/mL	28·0 (23·6–36·3)	29·2 (24·2–37·6)	28·6 (24·2–36·4)	28·8 (23·6–36·0)
Lumbar spine bone mineral density T score	–2·0 (1·4)	–1·9 (1·4)	–1·1 (1·6)	–0·9 (1·9)
Total hip bone mineral density T score	–1·6 (1·0)	–1·7 (1·0)	–1·0 (1·1)	–1·1 (1·0)
Previous osteoporotic fracture‡ since age 18 years	134 (53%)	136 (54%)	51 (35%)	49 (34%)
Prevalent vertebral fracture	80 (32%)	67 (26%)	26 (18%)	21 (14%)
Serum CTX concentration§, ng/L	140 (85–264)	205 (111–344)	230 (115–321)	259 (150–375)
Fracture Risk Assessment Tool (%)¶				
Major osteoporotic fracture (calculated with bone mineral density)	14·0 (8·1–23·1)	14·5 (7·8–24·5)	11·3 (7·3–17·2)	11·5 (7·6–17·9)
Hip fracture (calculated with bone mineral density)	4·2 (1·5–8·1)	4·4 (1·8–8·2)	2·7 (0·9–5·8)	3·1 (1·4–6·0)

Data are n (%), mean (SD), or median (IQR). *Patients could have more than one medical condition necessitating glucocorticoid therapy. †≥7·5 mg daily prednisone-equivalent dose. ‡Previous osteoporotic fracture included prevalent vertebral fractures and previous non-vertebral fractures, but excluded fractures associated with high trauma severity, pathological fractures, or fractures of the skull, facial bones, metacarpals, fingers, or toes. §Values for patients enrolled in the bone turnover marker substudy. ¶10-year probability of fracture (%) calculated with country-specific models adjusted for glucocorticoid use.

Table 1: **Baseline characteristics**

Role of the funding source

The study funder (Amgen) designed the study in collaboration with the corresponding author and WFL, and did the

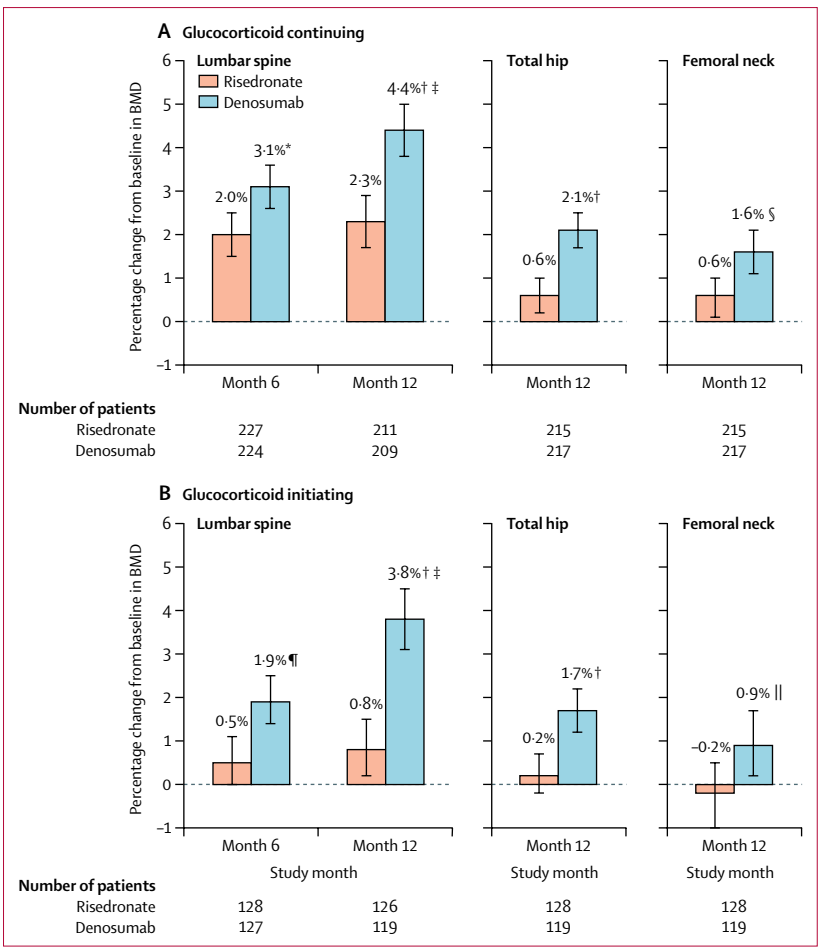

Figure 2: **Percentage change from baseline in BMD at the lumbar spine, total hip, and femoral neck in the glucocorticoid-continuing (A) and glucocorticoid-initiating (B) subpopulations**
Data are least-squares means with between-group comparison. Error bars show 95% CIs. Non-inferiority was assessed with respect to the difference in mean percentage change from baseline in lumbar spine BMD between groups (denosumab minus risedronate) at 12 months. BMD=bone mineral density. *p=0·002 compared with risedronate for superiority. †p<0·0001 compared with risedronate for superiority. ‡Non-inferiority was shown, because the lower bound of the two-sided 95% confidence interval was higher than the prespecified non-inferiority margin (–0·7 and –1·1 percentage points for the glucocorticoid-continuing and glucocorticoid-initiating subpopulations, respectively). §p=0·004 compared with risedronate for superiority. ¶p=0·0007 compared with risedronate for superiority. ||p=0·020 compared with risedronate for superiority.

analysis as per a prespecified statistical analysis plan. The funder was also involved in writing the first draft of the report. The corresponding author had full access to all the data in the study, and, together with AW (a statistician at Amgen), is responsible for the data and analyses. All authors were responsible for the decision to submit for publication. Agreements between Amgen and the investigators included provisions relating to study data confidentiality.

Results

Between March 28, 2012, and June 30, 2015, 795 patients (505 glucocorticoid-continuing patients and 290 glucocorticoid-initiating patients) were enrolled in the study (appendix). The last patient's 12-month visit was on June 29, 2016. 691 (87%) patients across both the glucocorticoid-continuing and the glucocorticoid-initiating subpopulations completed the first 12 months of the study (figure 1). The leading causes of study discontinuation were withdrawal of consent and adverse events in both subpopulations (figure 1). Baseline characteristics were balanced between treatment groups in both subpopulations (table 1; appendix). No difference in medication adherence was noted between treatment groups, with more than 75% of patients receiving 80% or more of the daily oral doses of active drug or placebo (data not shown).

Denosumab was non-inferior to risedronate for the percentage change from baseline in lumbar spine bone mineral density at 12 months in both the glucocorticoid-continuing (4·4% [95% CI 3·8–5·0] *vs* 2·3% [1·7–2·9]) and glucocorticoid-initiating (3·8% [3·1–4·5] *vs* 0·8% [0·2–1·5]) subpopulations (figure 2)—ie, the respective lower bounds of the two-sided 95% CIs were above the prespecified non-inferiority margins. Denosumab was also superior to risedronate for both secondary and exploratory bone mineral density endpoints (ie, lumbar spine, total hip, and femoral neck) at 12 months: the difference in mean percentage change from baseline in bone mineral density at 12 months between the denosumab and risedronate groups was 2·2% (95% CI 1·4–3·0) for the lumbar spine, 1·5% (1·0–2·1) for the total hip, and 1·0% (0·3–1·7) for the femoral neck in the glucocorticoid-continuing subpopulation. The corresponding values in the glucocorticoid-initiating subpopulation were 2·9% (2·0–3·9), 1·5% (0·8–2·1), and 1·1% (0·2–2·1), respectively. The prespecified per-protocol analysis of the primary endpoint showed consistent results (treatment difference at lumbar spine was 1·9% [95% CI 1·1–2·7] in the glucocorticoid-continuing group and 3·0% [2·0–4·1] in the glucocorticoid-initiating group; p<0·0001 for both). Sensitivity analyses to account for missing data for bone mineral density accorded with the superiority results for the prespecified analysis of denosumab versus risedronate in both subpopulations (data not shown). Concentrations of markers of bone turnover fell significantly more with denosumab than risedronate at nearly all timepoints (figure 3).

The patient incidence of adverse events, serious adverse events, fractures, and adverse events leading to discontinuation of treatment or discontinuation of the study were similar between groups (table 2). No serious adverse event was reported in more than 2% of patients in either treatment group. The most commonly reported serious adverse event in both treatment groups was pneumonia, which occurred in six (2%) of 384 patients in the risedronate group and five (1%) of 394 patients in the denosumab group (table 2). 111 (29%) patients in the risedronate group, and 105 (27%) in the denosumab group had infections (appendix). The incidence of serious infections in high-risk subgroups was also similar between groups: no serious infections were noted in the 17 patients in the denosumab group who were

also taking concomitant biologic medications, and two (7%) were noted in the 27 patients in the risedronate group who were taking biologics. Similarly, eight (4%) of 200 patients taking risedronate and six (3%) of 186 patients taking denosumab who were also taking concomitant biologics or any (biologic or non-biologic) immunosuppressants.

One positively adjudicated atypical femoral fracture occurred in the denosumab group, in a 60-year-old man who had been taking glucocorticoids for asthma for more than 30 years (the fracture occurred roughly 2 months after his second dose of denosumab). No positively adjudicated osteonecrosis of the jaw was reported. Osteoporosis-related fractures occurred in 23 (6%) of 397 patients in the risedronate group and 26 (6%) of 398 patients in the denosumab group (table 2). New and worsening vertebral fractures occurred in 15 (4%) of 342 patients in the risedronate group and ten (3%) of 333 patients in the denosumab group (table 2). Low-trauma non-vertebral fractures occurred in ten (3%) of 397 patients in the risedronate group and 17 (4%) of 398 patients in the denosumab group. One patient (<1%) in the denosumab group had positive binding, non-neutralising anti-denosumab antibodies.

Discussion

In this randomised, active-controlled trial, denosumab was both non-inferior and superior to risedronate, a commonly used bisphosphonate for glucocorticoid-induced osteoporosis, in increasing bone mineral density at the lumbar spine at 12 months in patients already taking or newly initiating glucocorticoid therapy. Superiority of denosumab over risedronate was also shown at the total hip. Denosumab was associated with a significant reduction in concentrations of markers of bone turnover compared with risedronate at nearly all timepoints. The safety profiles of denosumab and risedronate were similar, and denosumab was not associated with an increase in serious infections among patients who concomitantly used an additional biologic immunosuppressant, either alone or in combination with a non-biologic immunosuppressant (in addition to glucocorticoids). As expected, the glucocorticoid-initiating group was smaller than the glucocorticoid-continuing group, reflecting that fewer patients are starting therapy than already on sustained treatment. Glucocorticoid doses were higher in patients initiating glucocorticoids than in those already on treatment, which could contribute to the smaller increases in bone mineral density noted in the former.

We chose risedronate as the active comparator for three reasons. First, our study was modelled on a study[6] of zoledronic acid for treatment and prevention of glucocorticoid-induced osteoporosis, in which risedronate was the active comparator. Second, the non-inferiority margin for an active-controlled study is best derived from the treatment effect of the chosen active control in a placebo-controlled study in the same population of interest, and such data were available for risedronate.[7,16] Finally, risedronate was approved and available in all countries participating in this global study. The study design and non-inferiority margins for both subpopulations were based on two placebo-controlled trials with risedronate as the comparator in patients with glucocorticoid-induced osteoporosis, and a study of zoledronic acid versus risedronate in a similar population.[6,7,16]

In this study, denosumab and risedronate had similar clinical effects to those noted in osteoporosis studies both in postmenopausal women with osteoporosis and in glucocorticoid-induced osteoporosis. In a previous study[6] in glucocorticoid-induced osteoporosis in which zoledronic acid and risedronate were compared, a

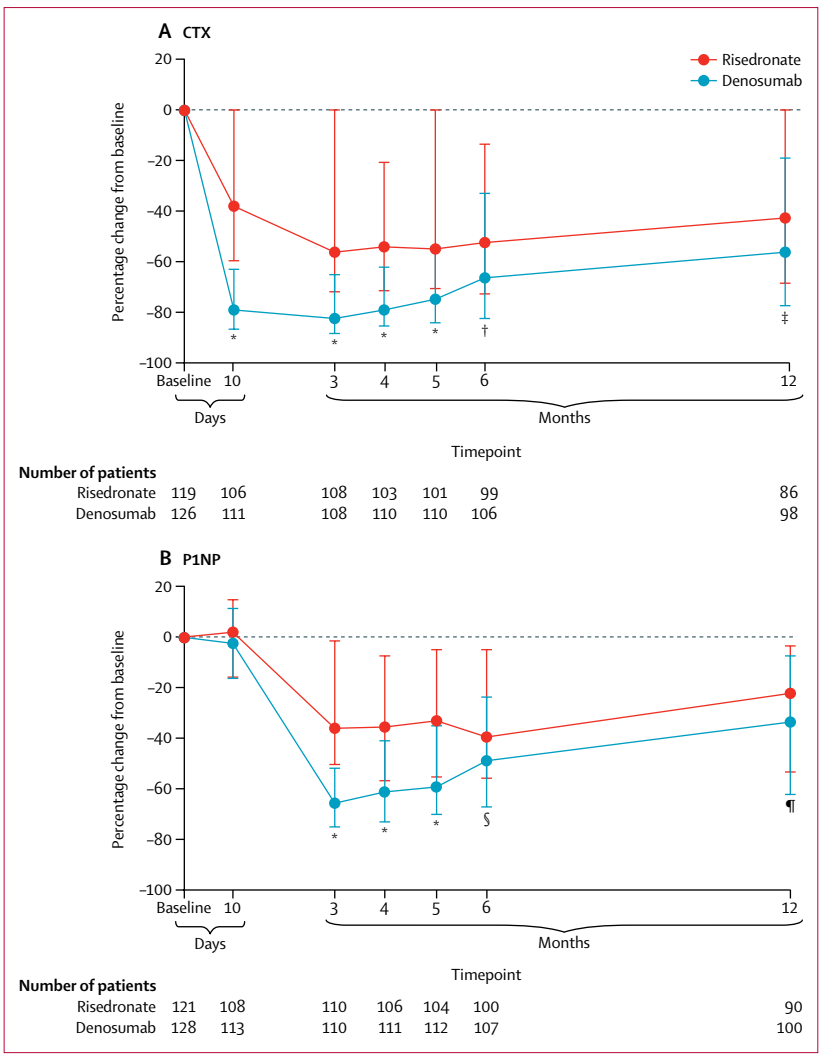

Figure 3: **Percentage change in CTX (A) and P1NP (B) from baseline to 12 months in the combined subpopulations (bone turnover marker substudy)**

Data are median values; error bars show IQRs. *p<0·0001 compared with risedronate. †p=0·021 compared with risedronate. ‡p=0·030 compared with risedronate. §p=0·004 compared with risedronate. ¶p=0·046 compared with risedronate.

	Risedronate (n=384)	Denosumab (n=394)
Overall	265 (69%)	285 (72%)
Serious adverse events	65 (17%)	63 (16%)
Leading to treatment discontinuation	29 (8%)	25 (6%)
Leading to study discontinuation	14 (4%)	15 (4%)
Fatal adverse events	2* (1%)	6 (2%)
Most frequent adverse events		
Back pain	17 (4%)	18 (5%)
Arthralgia	21 (5%)	17 (4%)
Hypertension	13 (3%)	15 (4%)
Most frequent serious adverse events		
Pneumonia	6 (2%)	5 (1%)
Cardiac failure	0 (0%)	3 (1%)
Transient ischaemic attack	0 (0%)	3 (1%)
Most frequent serious infections		
Pneumonia	6 (2%)	5 (1%)
Diverticulitis	1 (<1%)	1 (<1%)
Pyelonephritis acute	1 (<1%)	1 (<1%)
Bronchitis	2 (1%)	0 (0%)
Selected adverse events of interest		
Atypical femoral fracture	0 (0%)	1 (<1%)
Osteonecrosis of the jaw	0 (0%)	0 (0%)
Malignancy	3 (1%)	5 (1%)
Serious infections	15 (4%)	17 (4%)
Osteoporosis-related fractures	23/397 (6%)	26/398 (7%)
New and worsening vertebral fracture† (men)	3/100 (3%)	1/98 (1%)
New and worsening vertebral fracture† (women)	12/242 (5%)	9/235 (4%)
Premenopausal women	1/29 (3%)	0/33 (0%)
Postmenopausal women	11/209 (5%)	9/199 (5%)
Unknown	0/4 (0%)	0/3 (0%)
Non-vertebral fracture (low trauma)	10/397 (3%)	17/398 (4%)
Number of non-vertebral fractures by location	10	20
Rib	2	6
Humerus	3	3
Radius	2	1
Pelvis	1	4
Hip	1	1
Fibula	0	1
Femur distal	0	1
Foot	1	1
Metatarsus	0	2

All patients received at least one dose of risedronate or denosumab. Only treatment-emergent adverse events are listed. Osteoporosis-related fractures comprise new and worsening vertebral fracture and low-trauma non-vertebral fracture. Data are n, n (%), or n/N (%), where N is the total number of assessable patients. *Three additional deaths were reported in the risedronate group, but we could not confirm that these patients had taken at least one dose of oral risedronate, so they were excluded from the safety analysis. †Increase of at least one grade from baseline, assessed in patients who had spine radiographs taken on day 1 and at 12 months.

Table 2: **Summary of clinically relevant adverse events and osteoporosis-related fractures**

specific bone mineral density was not an inclusion criterion. Thus, the population of that study—and particularly the glucocorticoid-continuing population—had less severe bone disease than our study population. In that study, risedronate had similar effects on lumbar spine bone mineral density at 12 months to its effects in our study (2·7% and 0·6% increases in the glucocorticoid-continuing and glucocorticoid-initiating groups, respectively).[6] The increases in bone mineral density at the lumbar spine with denosumab in our study were similar to, or better than, those with alendronate and zoledronic acid seen in previous non-head-to-head studies in glucocorticoid-induced osteoporosis,[6,9] and those with denosumab in a study[12] in patients with rheumatoid arthritis not on glucocorticoids.[12]

Serious skin infections were reported more frequently in the denosumab group than in the placebo group in the pivotal fracture trial in postmenopausal women with osteoporosis,[13] and a higher rate of urinary tract infection was noted in patients taking denosumab after organ transplantation compared with those on no treatment.[20] However, in our study of patients with an inflammatory disease and taking glucocorticoids, including patients also taking biologics or any (biologic or non-biologic) immunosuppressants, the frequency of infection, including serious infection, was similar between treatment groups, although the study was not powered for this safety endpoint, and the number of patients taking concomitant biologic drugs was small. One atypical femoral fracture was recorded in the denosumab group. Atypical femoral fracture is an identified risk with denosumab treatment, and has been rarely reported in other studies.[21]

There is a need for primary and secondary prevention of fractures in patients on glucocorticoids, who have an estimated prevalence of more than 35% for vertebral fractures.[22] International guidelines[23–25] advocate initiation of osteoporosis therapy in nearly all patients studied in our clinical trial. Osteoporosis drugs approved for prevention and treatment of glucocorticoid-induced osteoporosis include antiresorptives (including bisphosphonates) and teriparatide. Treatment selection should be individualised and could take into account the pathophysiology of glucocorticoid-induced bone loss, which is characterised by transient increases in bone resorption and long-term reduction of bone formation at the tissue and cellular levels. Data from the USA, Canada, and Europe suggest that treatment rates among patients whom guidelines suggest should be taking bone-specific treatments for glucocorticoid-induced osteoporosis is often under 50%,[14,26,27] and bisphosphonate use is declining overall in many parts of the world.[28]

Therapies that need to be taken frequently (eg, daily) might result in low adherence.[29] Because denosumab does not embed into the bone matrix, its effect is fully reversible after discontinuation.[30] Thus, denosumab might be of particular relevance to premenopausal

women and patients with modestly reduced renal function, in whom concerns exist about the relative safety of long-term bisphosphonate use. In view of the fact that all anti-osteoporosis therapies have relative benefits and limitations for specific populations, the availability of more therapeutic choices is useful for clinicians.

Our study did not have adequate statistical power to detect fracture differences between treatment groups. Change from baseline in bone mineral density in the lumbar spine has been accepted by regulatory authorities as the primary efficacy assessment in clinical trials for glucocorticoid-induced osteoporosis in men and women after antifracture efficacy has been established in postmenopausal women with osteoporosis.[6–9,16] 3-year data from the FREEDOM trial[13] in women with postmenopausal osteoporosis showed that denosumab was associated with a reduced incidence of new vertebral fractures, non-vertebral fractures, and hip fractures compared with placebo. Because increases in bone mineral density were associated with reductions in fracture risk in FREEDOM, it is possible to extrapolate the antifracture efficacy of 60 mg denosumab given every 6 months to patients taking glucocorticoids, provided that increases in bone mineral density are similar across populations and fracture risk is similar. Notably, in our study, radiographs were taken to establish the effects of treatment on spine fractures, the most common fractures in patients with glucocorticoid-induced osteoporosis. Fracture incidence at 1 year was low in both groups, and similar overall.

A strength of this study was the large sample size. Our trial is among the largest randomised controlled trials in glucocorticoid-induced osteoporosis, and had a dropout rate of only 13% over 1 year, which is substantially lower than the 31% rate in the next most recent study in glucocorticoid-induced osteoporosis (of teriparatide).[9] Another strength was the active-comparator design,[6] although this approach limits the ability to detect a difference in fractures in a 1-year or 2-year study, because of the large number of patients that would be required to show superiority with respect to a fracture endpoint, especially in comparison with patients receiving active treatment. Furthermore, the study population is broadly generalisable to patients with similar underlying conditions that necessitate glucocorticoid use. Only one previous study[9] in glucocorticoid-induced osteoporosis has shown a significant difference in the frequency of fracture between groups on the basis of a small number of events captured via a semiquantitative vertebral assessment.[9] In that study, teriparatide was compared with alendronate over 3 years, and the population included a very high proportion of postmenopausal women.[9] Although the results of our study show superiority to risedronate in terms of bone mineral density, they do not fully inform the comparison of denosumab with other drugs or define denosumab's position in the hierarchy of drugs for glucocorticoid-induced osteoporosis. As noted previously, the established regulatory precedent for expansion of a treatment indication to include glucocorticoid-induced osteoporosis involves showing changes in bone mineral density similar to those noted in postmenopausal women treated for osteoporosis, which allows for bridging of antifracture efficacy between the two proposed treatment populations. Notably, the results of a meta-analysis[31] showed that the effects of bisphosphonates on the incidence of vertebral and non-vertebral fractures in patients with glucocorticoid-induced osteoporosis were similar to those noted in postmenopausal osteoporosis.

In conclusion, denosumab was more efficacious than risedronate for the improvement of bone mineral density, an important predictor of fractures, in patients newly starting or continuing glucocorticoids who were at substantial risk of fracture. Denosumab could be a useful addition to the treatment armamentarium for glucocorticoid-induced osteoporosis.

Contributors

KGS and WFL contributed to the design of the study in collaboration with the study funder. KGS, PG, JDA, ODM, RE, RC, and WFL acquired data. AW was the study statistician; KGS and AW were responsible for the data and analyses. KGS, RBW, AW, NP, and WFL interpreted the data. KGS developed the first draft of the report with support from the funder; all authors contributed to subsequent drafts of the report.

Declaration of interests

KGS has received research grants and consulting fees from Amgen, Merck, and Radius, and consulting fees from Lilly. RBW, AW, and NP are employees of, and hold stock and stock options in, Amgen. PG has received research grants and consulting fees from Abbott, Amgen, Bristol-Myers Squibb, MSD, Novartis, Pfizer, Roche, UCB, and Will. JDA has received research grants and consulting fees from, and is on a speakers' bureau for Amgen, Eli Lilly, Merck, and Pfizer, and has a non-remunerative position of influence with the International Osteoporosis Foundation and Osteoporosis Canada. ODM has received research grants from Amgen and GSK. RE is on a speakers' bureau for Amgen and has received consulting fees from Amgen. RC has received research grants from Amgen, Chugai-Roche, Merck, and MSD, and consulting fees from AbbVie, Amgen, Bristol-Myers Squibb, Chugai-Roche, Eli Lilly, Merck, MSD, Nordic, Pfizer, Radius, Sandoz, and UCB. WFL has received consulting fees from Amgen, Eli Lilly, MSD, and Novartis.

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