RHEUMATOLOGY

doi:10.1093/rheumatology/kes410
Advance Access publication 30 January 2013

Original article

Effect on bone turnover markers of once-yearly intravenous infusion of zoledronic acid versus daily oral risedronate in patients treated with glucocorticoids

Jean-Pierre Devogelaer[1], Philip Sambrook[2,†], David M. Reid[3], Stefan Goemaere[4], Sophia Ish-Shalom[5], Julien Collette[6], Guoqin Su[7], Christina Bucci-Rechtweg[7], Philemon Papanastasiou[8] and Jean-Yves Reginster[9]

Abstract

Objective. Long-term glucocorticoid use is accompanied by rapid bone loss; however, early treatment with bisphosphonates prevents bone loss and reduces fracture risk. The aim of this study was to examine the effects of two bisphosphonates, i.v. zoledronic acid (ZOL) versus oral risedronate (RIS), on bone turnover markers (BTMs) in subjects with glucocorticoid-induced osteoporosis (GIO).

Methods. Patients were randomly stratified according to the duration of pre-study glucocorticoid therapy [prevention subpopulation (ZOL, $n = 144$; RIS, $n = 144$) $\leqslant 3$ months, treatment subpopulation (ZOL, $n = 272$; RIS, $n = 273$) >3 months]. Changes in β-C-terminal telopeptides of type 1 collagen (β-CTx), N-terminal telopeptide of type I collagen (NTx), procollagen type 1 N-terminal propeptide (P1NP) and bone-specific alkaline phosphatase (BSAP) from baseline were measured on day 10 and months 3, 6 and 12.

Results. At most time points, there were significantly greater reductions ($P < 0.05$) in the concentrations of serum β-CTx, P1NP and BSAP and urine NTx in subjects on ZOL compared with RIS in both males and females of the treatment and prevention subpopulations. In pre- and post-menopausal women, there were significantly greater reductions in the concentrations of BTMs with ZOL compared with RIS. At 12 months, ZOL had significantly greater reductions compared with RIS ($P < 0.05$) for β-CTx, P1NP, BSAP and NTx levels, independent of glucocorticoid dose.

Conclusions. Once-yearly i.v. infusion of ZOL 5 mg was well tolerated in different subgroups of GIO patients. ZOL was non-inferior to RIS and even superior to RIS in the response of BTMs in GIO patients.

Trial registration: ClinicalTrials.gov, http://clinicaltrials.gov, NCT00100620.

Key words: zoledronic acid, risedronate, glucocorticoids, glucocorticoid-induced osteoporosis, bone turnover markers.

CLINICAL SCIENCE

[1]Université Catholique de Louvain, Brussels, Belgium, [2]University of Sydney, Sydney, NSW, Australia, [3]University of Aberdeen, Aberdeen, UK, [4]Universitair Ziekenhuis Gent, Gent, Belgium, [5]Bone and Mineral Metabolism Unit, Rambam Health Care Campus, Technion Faculty of Medicine, Haifa, Israel, [6]University of Liège, CHU - Bone & Cartilage Markers Lab, Liège, Belgium, [7]Novartis Pharmaceuticals, East Hanover, NJ, USA, [8]Novartis Pharma AG, Basel, Switzerland and [9]University of Liège, Liège, Belgium.

Submitted 8 August 2012; revised version accepted 5 December 2012.

Correspondence to: Jean-Pierre Devogelaer, Université Catholique de Louvain, UCL5390, B-1200 Brussels, Belgium.
E-mail: devogelaer@ruma.ucl.ac.be or jean-pierre.devogelaer@uclouvain.be

[†]Deceased.

Introduction

Glucocorticoid-induced osteoporosis (GIO) is the most common form of secondary osteoporosis, with fractures occurring in 30–50% of patients receiving long-term glucocorticoid (GC) therapy. Although GCs have favourable therapeutic effects in a variety of inflammatory diseases, they cause significant bone loss and increase bone fragility and associated bone fractures among long-term users in a GC dose-dependent manner [1–4]. Men and post-menopausal women are at greatest risk, and there

is a particularly high prevalence of symptomatic and asymptomatic vertebral fractures in post-menopausal women (37%, with two or more asymptomatic vertebral fractures reported in 14.5% of patients) on long-term GC therapy [5–7].

Although established treatment is available in many countries, and clinical guidelines recommend bisphosphonates for prevention and treatment of GIO, access to such treatments is not available for many patients, as the severity of this condition has often been underestimated by the medical community. Many hospitalized patients who should have received treatments such as bisphosphonates, HRT or other medications including vitamin D, calcium and calcitonin to prevent GIO, often do not receive them. A survey on patients taking oral corticosteroids has shown that only 8% of hospitalized patients and 14% of those in general practice were receiving prophylactic medication to prevent bone loss [8, 9].

Prevention and treatment for GIO is currently best established for bisphosphonates [10, 11]. In placebo-controlled trials, bisphosphonates such as risedronate (RIS) and alendronate have been shown to increase bone mineral density (BMD) and reduce the risk of vertebral fractures in patients initiating corticosteroids or receiving such treatment for a longer period of time [12–16].

Regulatory approval for the treatment and prevention of GIO has been granted for bisphosphonates, including the oral agents RIS and alendronate and i.v. zoledronic acid (ZOL). In clinical practice, compliance with daily oral bisphosphonate therapy is reportedly low due to difficulties in adhering to the strict dosing regimen of posture and fasting [17], which may pose particular issues in those taking GCs concomitantly with multiple other medications. In addition, the low bioavailability of oral bisphosphonates and poor tolerability due to upper gastrointestinal adverse events are of concern. Up to 50% of patients fail to adhere or comply with a daily oral treatment regimen within 1 year, which has been associated with higher fracture rates [18].

Once-yearly i.v. infusion of ZOL increases BMD and reduces fracture risk in women with post-menopausal osteoporosis [19]. It also reduces subsequent fractures and increases survival rate in patients who have had a prior low-trauma hip fracture [20]. ZOL is contraindicated in patients with creatinine clearance <35 ml/min or in patients with evidence of acute renal impairment. Increasing the infusion time for ZOL from 5 to 15 min has been shown to have fewer adverse effects on renal function. Therefore, a minimum infusion time of 15 min is strongly recommended. The renal safety of ZOL has been shown in osteoporotic post-menopausal women, provided the infusions lasted at least 15 min [21]. The first infusion of ZOL is associated with acute flu-like symptoms, but these are generally mild and transient and disappear with subsequent infusions [22]. However, although RIS has been shown to substantially reduce the occurrence of non-vertebral–non-hip fractures, taking into consideration the incidence of vertebral, hip and non-vertebral–non-hip fractures and their impact on cost and quality of life, ZOL has been demonstrated to be of great benefit [23]. Furthermore, ZOL 5 mg has been shown to be cost effective in post-menopausal osteoporosis in Finland, Norway and the Netherlands [24]. The assessment of response to bisphosphonate therapy was reported to be very useful with bone turnover markers (BTMs) that are early indicators of bone formation and resorption [25, 26]. However, there are few studies with the aim of evaluating changes in BTMs following GC administration [27]. The authors have previously reported the role of ZOL in preventing and maintaining BMD in patients on GC therapy [28]. This study reports the effects of a single once-yearly i.v. infusion of ZOL 5 mg versus daily oral RIS 5 mg on BTMs in varied subpopulations of patients with GIO.

Methods

Participants

The study included patients (men and women) between 18 and 85 years of age being treated with at least 7.5 mg oral prednisone daily (or equivalent systemic GCs) and expected to continue GCs for at least another 12 months. Participants were enrolled from 54 centres in 16 countries of North and South America, Asia, Australia and Europe. They were selected from two cohorts: those who started taking GCs within the last 3 months and those who had been taking GCs for more than 3 months. They were required to have at least three evaluable vertebrae in the lumbar spine region (L1–L4) to be eligible for inclusion, determined by lumbar spine radiography screening. Subjects previously treated with bisphosphonates (except according to the washout schedule at the time of randomization: 2 years if used for $\geqslant 48$ weeks; 1 year if used for >8 weeks but <48 weeks; 6 months if used for >2 weeks but $\leqslant 8$ weeks; 2 months if used for $\leqslant 2$ weeks), sodium fluoride or elemental fluoride (>1500 mg), strontium ranelate, HRT (except low-dose vaginal oestrogen such as 17β-oestradiol $\leqslant 0.2$ mg/day or oestrophitate $\leqslant 1.5$ mg/day), calcitonin or calcitriol (>1.5 μg/week) were excluded. Patients were also excluded if they were pregnant, had a history of cancer, osteogenesis imperfecta, multiple myeloma, Paget's disease or renal impairment (creatinine clearance <30 ml/min) or a serum 25-hydroxyvitamin D concentration <29 nmol/ml. Written informed consent was obtained from all subjects before entering the study. The study was approved by the local institutional review boards/independent ethics committee/research ethics boards (for names of the local institutional review boards/independent ethics committee/research ethics boards, please see supplementary data, available at *Rheumatology* Online). The study was conducted according to the ethical principles of the Declaration of Helsinki. The trial identifier for ClinicalTrials.gov is NCT00100620.

Study design

This was a *post hoc* analysis of a multinational, multicentre, 12-month, double-blind, double-dummy, stratified,

active controlled parallel group study where patients were randomly selected to receive either once-yearly i.v. infusion of ZOL 5 mg and daily oral placebo capsules or daily oral RIS 5 mg capsules and a once-yearly i.v. infusion of placebo [28]. Subjects received 5 mg of ZOL or placebo as a slow peripheral i.v. infusion of 100 ml over 15 min. RIS or matching oral placebo capsules were taken daily at least 30 min before the first food or drink of the day. All patients received daily supplemental vitamin D at a dose between 400 and 1200 IU and elemental calcium 1000 mg/day starting up to 28 days (visit 1) before the infusion and continuing throughout the trial. Patients were classified according to the duration of their pre-study GC therapy (prevention subpopulation $\leqslant$3 months, treatment subpopulation $>$3 months), gender (male and female) and menopausal status in females (pre-menopausal and post-menopausal). The study was originally designed to show non-inferiority of ZOL to RIS for lumbar spine BMD and the results were published [28].

Markers of bone turnover

BTMs were assessed as secondary endpoints for this trial. Markers for bone resorption [β-C-terminal telopeptide of type I collagen (β-CTx), N-terminal telopeptide of type I collagen (NTx)] and formation [procollagen type I amino-terminal propeptide (P1NP), bone-specific alkaline phosphatase (BSAP)] were measured at baseline. The relative changes of BTMs from baseline at different time intervals of 10 days and 3, 6 and 12 months were measured. Specific serum tests were performed for β-CTx, P1NP and BSAP analysis. Blood was drawn from patients within 28 days before the first dose of study drug was administered at baseline and at all subsequent visits until month 12. In the prevention arm of this study, baseline samples were drawn after patients received their first dose of GC. Urinary NTx and creatinine were measured on second morning-voided urine samples. Serum and urine samples used to assess BTMs were collected after an overnight fast of at least 8 hours. Calcium and vitamin D were not to be taken on the morning prior to a scheduled blood draw. Patients were instructed to take their oral study medication as usual.

Serum β-CTx was measured using electrochemiluminescence immunoassay (Elecsys Immunoassay System, Roche, Basel, Switzerland) [coefficient of variation (CV) within assay $<$7%, between assay $<$10%]; P1NP was measured using UniQ PINP RIA (Orion Diagnostica Oy, Espoo, Finland; CV within and between assay $<$8%) and BSAP was measured by using immunoradiometric assay with Tandem-R Ostase (Beckman Coulter, Fullerton, CA, USA) (CV within assay $<$8%, between assay $<$6%).

Urine NTx was measured using ELISA (Osteomark, Ostex International Inc., Seattle, WA, USA; CV within assay $<$12%, between assay $<$8%). The NTx results were expressed in nanomoles of bone collagen equivalent (BCE) per litre and were corrected by creatinine concentration (mM) to be expressed in nanomoles BCE per millimole. Urine creatinine was measured by the modified Jaffe method using a modular analyser (Roche Diagnostics, Mannheim, Germany) [29, 30]. All these analyses were performed at the Bone and Cartilage Markers Laboratory at the University of Liège (Liège, Belgium).

At the end of the study, patients were given a patient preference questionnaire to determine their preference for different treatment modalities. Patients were asked which treatment was more convenient, more satisfying, which they would be more willing to take for a long period of time and overall preference. Responses were evaluated according to subpopulation and treatment.

Statistical analysis

BTMs were analysed in the modified intention-to-treat group, which consisted of all patients in the intention-to-treat population who received study drug and who had an evaluable baseline assessment for the endpoint of interest. The biomarker parameters were analysed based on the ratio of the post-baseline value relative to baseline using a $\log_e$ transformation at each visit, which allows for an interpretation that is similar to the analysis of percentage change from baseline. A three-way analysis of covariance (ANCOVA) with treatment group, study region and $\log_e$ (baseline value) was performed on the log-transformed ratio (visit/baseline) at each post-baseline time point (day 10 and months 3, 6 and 12) in each subpopulation. Treatment-by-factor interactions with gender, menopausal status and GC dose at the corresponding study time (i.e. GC dose at the time of randomization and mean GC dose during the study and at the end of treatment) for biochemical markers of bone turnover were investigated using a three-way ANCOVA model. To assess the use of prednisone at randomization, during the study and at the end of study for the biochemical markers, the different types of oral GCs were transformed to a prednisone-equivalent dose. For statistical analyses, subjects were grouped into low, medium and high dose of daily prednisone-equivalent GC according to the following dose categories: $<$7.5, 7.5 to $<$12, $>$12 mg/day, respectively. For statistical comparisons, a *P*-value of 0.05 was considered statistically significant.

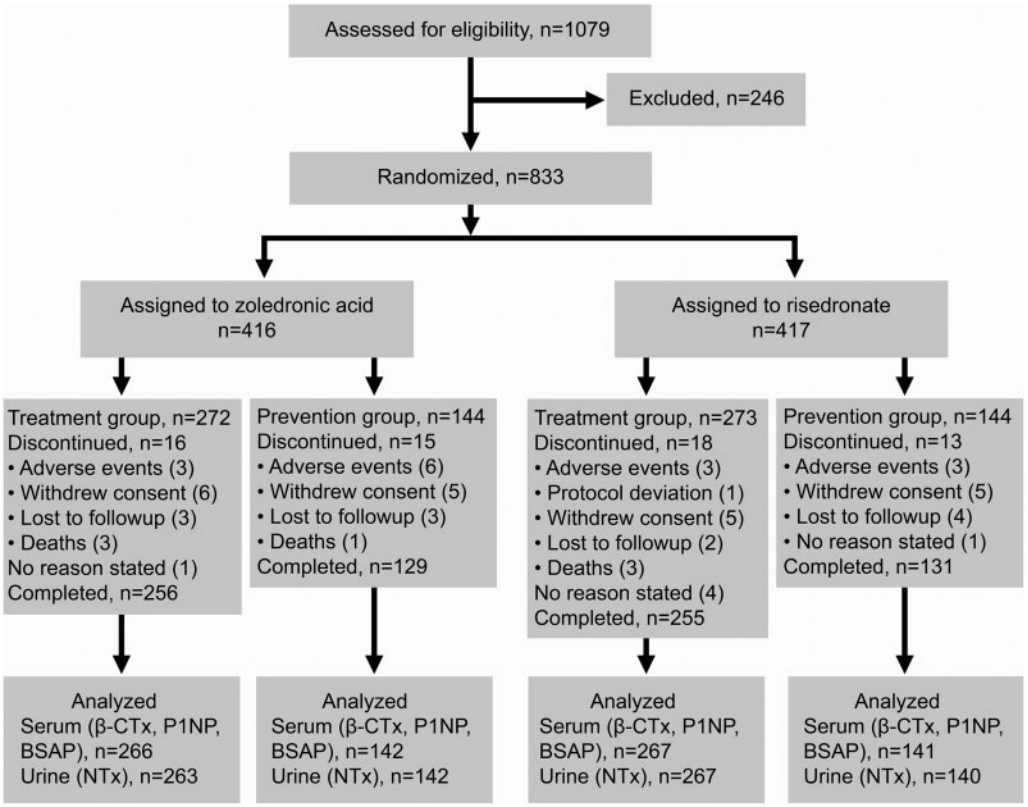
Results

Of the 833 patients randomly selected, 416 received ZOL and 417 received RIS (Fig. 1). These groups were further divided into treatment (ZOL, $n = 272$; RIS, $n = 273$) and prevention subpopulations (ZOL, $n = 144$; RIS, $n = 144$). Overall, 771 subjects (93%) completed the trial.

Baseline characteristics

Baseline characteristics of the subjects were well balanced between the ZOL and RIS groups (Table 1). Of the 568 women randomized, 373 were post-menopausal. In the ZOL group, 5 men and 13 women and in the RIS group 5 men and 7 women had a history of vertebral fractures at baseline. The commonly reported active medical conditions at baseline were RA and SLE (Table 1). The prednisone-equivalent dose of GCs was similar for both

FIG. 1 Schematic representation of participant disposition for the study.



β-CTx, NTx, P1NP and BSAP were analysed for both treatment and prevention subpopulations at various time points.

the ZOL and RIS treatment groups in the treatment and prevention subpopulations (Table 1). The treatment subpopulation has significantly lower β-CTx and significantly higher BSAP and P1NP compared with the prevention subpopulation ($P < 0.05$). There was no significant difference between the two subpopulations in the baseline serum values for NTx (Supplementary Table 1, available at *Rheumatology* Online).

Bone resorption markers

The post-baseline analysis showed that the concentrations of BTMs (serum β-CTx and urinary NTx) consistently decreased from baseline, at all time points, in both male and female subgroups of ZOL and RIS (Fig. 2A and B). There were significantly greater reductions ($P < 0.05$) in serum β-CTx and urine NTx levels in both male and female subjects on ZOL therapy compared with those on RIS therapy in the treatment and prevention subpopulations at day 10 and months 3, 6 and 12, with the exception of NTx for the male prevention subpopulation at month 12.

Bone formation markers

There were significantly greater reductions ($P < 0.05$) in both serum P1NP and BSAP concentrations with ZOL treatment compared with RIS treatment for both male and female subgroups at different post-baseline time points (Fig. 2C and D). Serum P1NP levels also decreased more significantly with ZOL therapy compared with RIS at all post-baseline time points in females of the prevention subpopulation. For the male and female subgroups of the treatment subpopulation who were on RIS therapy, P1NP concentrations did not change much from baseline to day 10; however, they decreased significantly at months 3, 6 and 12. In the prevention subpopulation, BSAP levels were reduced more significantly with ZOL at months 3 and 6 in females and at month 3 in males (Fig. 2D).

Menopausal status

Analyses of results on the basis of menopausal criteria demonstrated that there was a significantly greater reduction in the concentrations of the biomarkers with ZOL treatment compared with RIS in both pre- and postmenopausal women (Fig. 3A–D).

Prednisone-equivalent dose effect

The influence of prednisone-equivalent dose (<7.5, 7.5 to <12 and >12 mg/day) on the response of ZOL and RIS to biochemical markers of bone turnover was analysed at different time points. Results of the treatment effect at 12 months revealed that ZOL-treated subjects had significantly greater reductions in β-CTx, NTx, BSAP and P1NP compared with RIS-treated subjects ($P < 0.05$) for both treatment and prevention subpopulations, which was

Table 1 Baseline characteristics of the treatment and prevention subpopulations

Characteristics	Treatment subpopulation		Prevention subpopulation	
	ZOL ($n = 272$)	RIS ($n = 273$)	ZOL ($n = 144$)	RIS ($n = 144$)
Females, *n* (%)	185 (68)	183 (67)	100 (69)	100 (69)
Post-menopausal females, *n* (%)	118 (64)	117 (64)	69 (69)	69 (69)
Males, *n* (%)	87 (32)	90 (33)	44 (31)	44 (31)
Age (years), mean (S.D.)	53.2 (14)	52.7 (13.7)	56.3 (15.4)	58.1 (14.7)
Age group (years), *n* (%)				
<35	29 (10.7)	30 (11)	15 (10.4)	12 (8.3)
35–50	82 (30.1)	89 (32.6)	33 (22.9)	27 (18.8)
51–64	96 (35.3)	94 (34.4)	45 (31.3)	50 (34.7)
65–74	52 (19.1)	48 (17.6)	35 (24.3)	35 (24.3)
⩾75	13 (4.8)	12 (4.4)	16 (11.1)	20 (13.9)
Serum β-CTx concentration (ng/ml), median (IQR)				
Males	0.35 (0.27)	0.37 (0.26)	0.42 (0.26)	0.45 (0.24)
Females	0.32 (0.26)	0.31 (0.27)	0.41 (0.26)	0.39 (0.31)
RA[a]	0.38 (0.25)	0.35 (0.30)	0.47 (0.32)	0.40 (0.31)
SLE[b]	0.26 (0.20)	0.25 (0.30)	0.28 (0.34)	0.31 (0.30)
Serum BSAP concentration (ng/ml), median (IQR)				
Males	8.16 (4.62)	8.52 (4.34)	7.05 (2.17)	6.80 (3.19)
Females	7.98 (4.44)	8.06 (3.63)	7.79 (4.12)	6.93 (3.66)
RA[a]	8.75 (4.56)	8.78 (4.0)	8.08 (4.79)	7.39 (5.34)
SLE[b]	7.43 (3.21)	7.98 (4.34)	7.68 (2.51)	6.93 (4.06)
Serum P1NP concentration (ng/ml), median (IQR)				
Males	38.44 (24.42)	33.32 (24.88)	27.07 (18.49)	24.03 (24.30)
Females	38.50 (29.06)	40.34 (27.22)	37.72 (31.16)	30.69 (22.47)
RA[a]	45.10 (24.48)	45.14 (28.75)	45.49 (24.92)	35.79 (26.86)
SLE[b]	35.52 (20.43)	36.11 (17.35)	28.81 (40.86)	24.98 (12.87)
Urine NTx concentration (nmol BCE/mmol creatinine), median (IQR)				
Males	42.34 (27.84)	43.09 (26.85)	46.67 (43.09)	44.87 (31.98)
Females	38.68 (32.37)	42.19 (32.55)	55.03 (45.51)	48.36 (37.51)
RA[a]	50.18 (33.19)	45.01 (30.23)	54.19 (48.7)	47.46 (39.02)
SLE[b]	31.69 (24.41)	34.45 (45.41)	45.47 (59.09)	55.49 (61.51)
Lumbar spine T-score, mean (S.D.)	−1.34 (1.34)	−1.4 (1.28)	−0.95 (1.45)	−0.91 (1.44)
Prednisone-equivalent dose (mg/day), *n* (%)				
<7.5	3 (1.1)	3 (1.1)	3 (2.1)	-
7.5 to <12	193 (71.0)	204 (74.7)	78 (54.2)	74 (51.4)
⩾12	76 (27.9)	66 (24.2)	63 (43.87)	70 (48.6)
History of most recent vertebral fracture, *n* (%)				
Males	4 (4.6)	3 (3.3)	1 (2.3)	2 (4.5)
Females	8 (4.3)	7 (3.8)	5 (5)	0
Baseline serum 25-OH vitamin D level (nmol/l)				
Nichols method[c], mean (S.D.)	62.12 (30.30)	64.29 (36.81)	59.92 (26.40)	54.92 (20.87)
DiaSorin method[c], mean (S.D.)	44.39 (15.80)	44.50 (19.34)	54.20 (19.86)	57.44 (39.13)

IQR: interquartile range. [a]Patients with active RA. [b]Patients with active SLE. [c]Prior to August 2005, the Nichols assay was used to measure vitamin D except when the value was <29.9 nmol/l, in which case the DiaSorin assay was used. Starting in August 2005, only the DiaSorin assay was used; a repeat test was allowed. The last value prior to randomization is presented for each assay, so some values may be below the inclusion limit.

independent of prednisone-equivalent dose at the end of the study (Table 2).

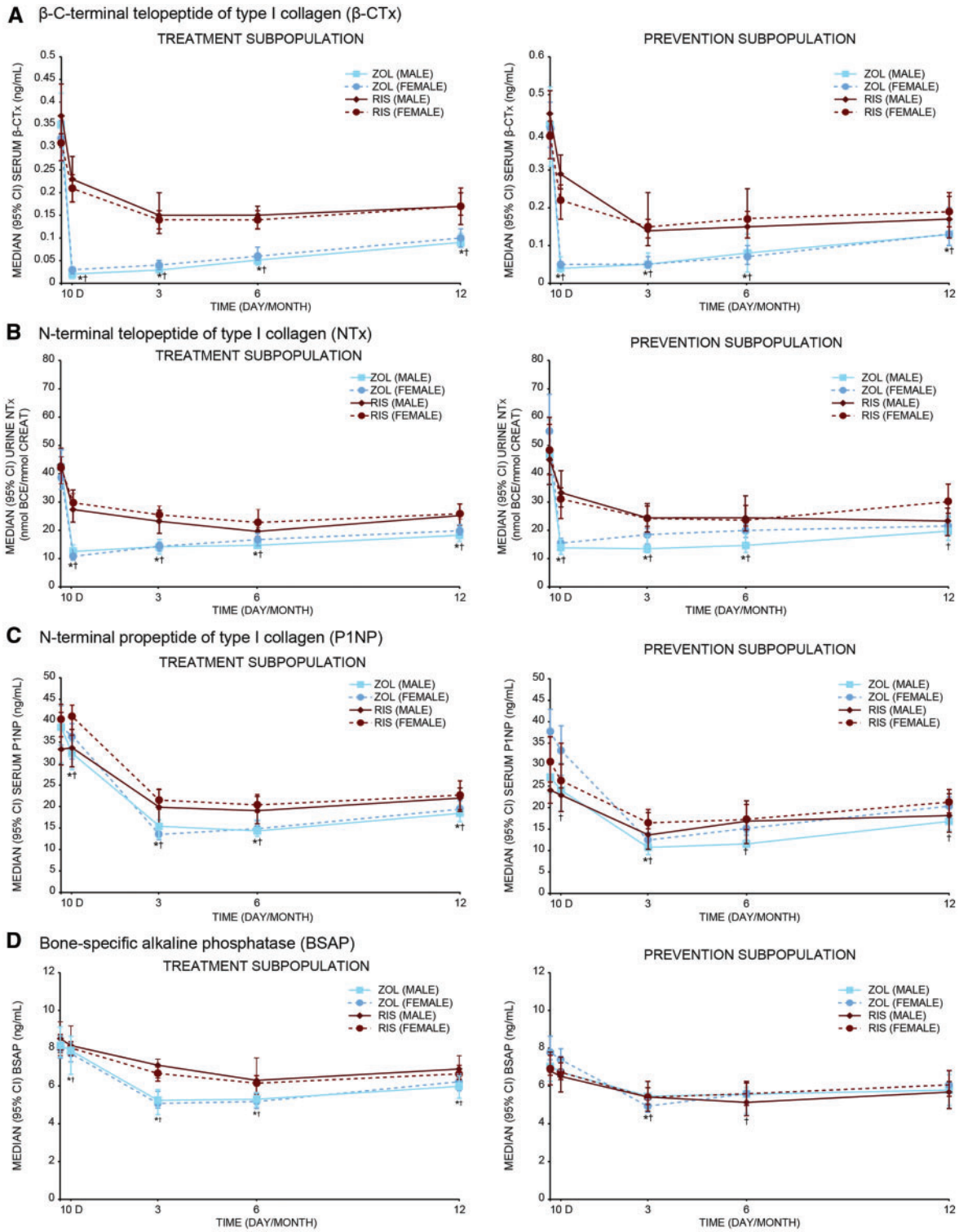
Patient preference for treatment regimen

The results on patient preference (based on the responses to the questionnaire) for treatment regimen are summarized in Table 3. For all four types of questionnaires, a once-yearly infusion was preferred by the majority of patients regardless of subpopulation, gender or menopausal status.

Discussion

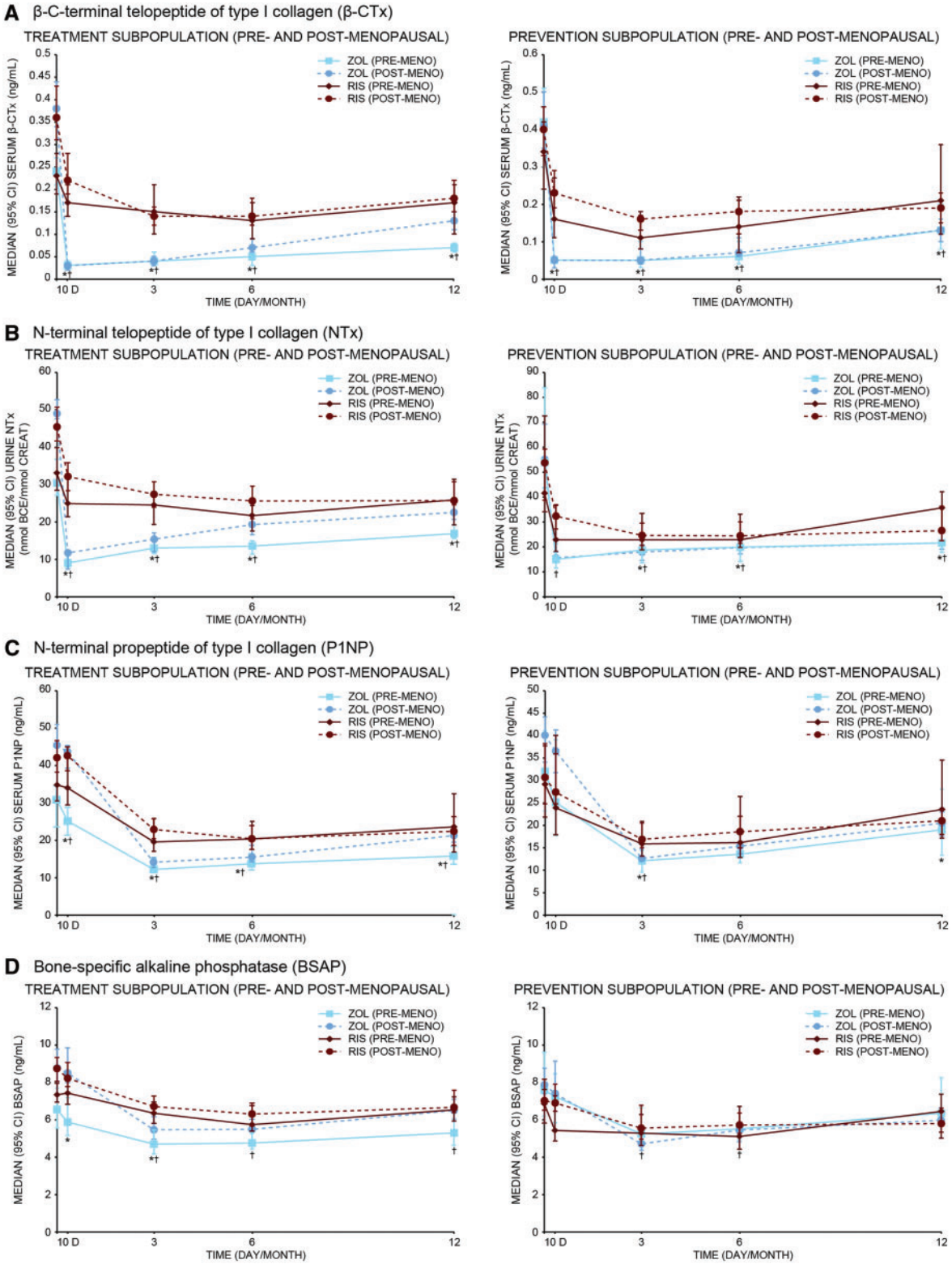
A single infusion of ZOL has been shown to provide greater increases and maintenance of BMD and a more rapid and substantial decrease in BTMs than

FIG. 2 Changes in the concentrations (median) of bone resorption and bone formation markers.



Bone resorption markers [serum β-CTx (**A**) and urine NTx (**B**)] and bone formation markers [serum P1NP (**C**) and serum BSAP (**D**)], overtime in the male and female subgroups of the treatment and prevention subpopulations. $P < 0.05$ shows statistical significance; $^{*}P < 0.05$ (male subjects), $^{\dagger}P < 0.05$ (female subjects). Error bars represent 95% CIs.

FIG. 3 Changes in BTM concentrations (median) over time in the pre- and post-menopausal female subgroups of the treatment and prevention subpopulations.



(**A**) β-CTx, (**B**) NTx, (**C**) P1NP and (**D**) BSAP. BTM analyses were done with $\log_e$ ratios of drug group to baseline with an ANCOVA model adjusted for drug group, study region and $\log_e$ of baseline. *P*-values compare changes in BTMs relative to baseline between study drugs. $P < 0.05$ shows statistical significance; $^{*}P < 0.05$ (pre-menopausal), $^{\dagger}P < 0.05$ (post-menopausal). Error bars represent 95% CIs.

TABLE 2 Between-treatment comparison at 12 months for β-CTx, NTx, BSAP and P1NP with glucocorticoid (GC) doses at the end of treatment by subpopulation

GC dose (mg/day)	*n* (ZOL/RIS)	Relative treatment effect[a]	95% CI of ratio	Within GC dose *P*-value	Treatment by GC dose interaction *P*-value
β-CTx (treatment subpopulation)					
<7.5	53/41	0.62	0.45, 0.85	0.004*	0.89
7.5 to <12	150/155	0.59	0.49, 0.70	<0.0001*	
⩾12	43/44	0.65	0.47, 0.9	0.0105*	
β-CTx (prevention subpopulation)					
<7.5	40/41	0.65	0.46, 0.92	0.0156*	0.82
7.5 to <12	63/64	0.61	0.49, 0.76	<0.0001*	
⩾12	16/18	0.46	0.22, 0.94	0.0336*	
NTx (treatment subpopulation)					
<7.5	52/42	0.89	0.69, 1.14	0.3374	0.33
7.5 to <12	151/158	0.79	0.70, 0.90	0.0003*	
⩾12	44/46	0.71	0.57, 0.88	0.0023*	
NTx (prevention subpopulation)					
<7.5	39/43	0.80	0.62, 1.03	0.0814	0.95
7.5 to <12	66/63	0.76	0.64, 0.91	0.0037*	
⩾12	18/19	0.67	0.48, 0.93	0.0197*	
BSAP (treatment subpopulation)					
<7.5	55/42	0.96	0.83, 1.10	0.5470	0.20
7.5 to <12	152/160	0.86	0.80, 0.93	0.0001*	
⩾12	45/45	0.97	0.85, 1.11	0.6735	
BSAP (prevention subpopulation)					
<7.5	40/44	0.88	0.75, 1.03	0.1141	0.62
7.5 to <12	66/65	0.92	0.83, 1.03	0.1425	
⩾12	18/19	0.99	0.80, 1.22	0.9058	
P1NP (treatment subpopulation)					
<7.5	55/42	0.88	0.71, 1.09	0.2407	0.28
7.5 to <12	152/159	0.78	0.71, 0.87	<0.0001*	
⩾12	45/45	0.91	0.76, 1.10	0.3334	
P1NP (prevention subpopulation)					
<7.5	40/44	0.90	0.73, 1.11	0.3106	0.31
7.5 to <12	66/65	0.91	0.79, 1.06	0.2419	
⩾12	18/18	0.67	0.46, 0.98	0.0386*	

[a]Relative treatment effect: the exponential of the least squares mean (LSM) difference on the $\log_e$ ratio scale. For values <1, ZOL has a greater reduction than RIS. *Significant $P < 0.05$.

daily RIS [28]. The present analyses demonstrated that 5 mg of ZOL given once yearly as a single i.v. infusion is able to exert its effect on BTMs in patients with GIO regardless of gender, menopausal status and independent of the GC dose received.

Although GIO is generally regarded as a condition with low bone turnover, especially in patients with chronic GC use, our baseline markers were generally not that low. However, markers of resorption such as β-CTx were higher in the prevention arm versus the treatment arm at baseline, consistent with results of previous studies [31, 32]. This observation likely reflects that the underlying inflammatory disease for which the GCs are being prescribed is driving bone resorption. In contrast, levels of the bone formation marker serum P1NP were lower at baseline in the prevention arm, suggesting that the underlying inflammatory disease is itself contributing to the negative balance of bone resorption and formation.

In the present study, once-yearly ZOL 5 mg i.v. infusion was associated with statistically significant reductions in BTMs in multiple subgroups of patients with GIO. The concentrations of bone resorption markers (β-CTx and NTx) were rapidly reduced at different post-baseline time points by both treatments (RIS and ZOL), although the effect was more rapid and more marked for ZOL. Similar data from a male osteoporosis study recently reported a more pronounced effect of ZOL compared with oral alendronate in the reduction of BTM concentrations at different post-baseline time points [33]. In this study, while there was a decrease in markers of bone formation (P1NP and BSAP), the effect was delayed. These results indicate a significant decrease in the elevated bone resorption rate and only a slightly higher inhibition of the already low bone formation rate by ZOL [34]. As reported in previous studies on ZOL [19, 20, 28], the nadir for BTMs is observed at the time of the earliest assessment at approximately day

Table 3 Patient preferences for treatment regimen [based on ITT population (treatment and prevention subpopulations)]

	Patient preference	More convenient, *n* (%)	More satisfying, *n* (%)	More willing to take for a long period of time, *n* (%)	Overall preference, *n* (%)
Treatment					
Male (161)	Once a year i.v.	133 (82.6)	127 (78.9)	137 (85.1)	134 (83.2)
	Once daily pill	12 (7.5)	15 (9.3)	15 (9.3)	15 (9.3)
	Both are equal	15 (9.3)	19 (11.8)	9 (5.6)	12 (7.5)
Female (353)	Once a year i.v.	286 (81.0)	278 (78.8)	293 (83.0)	299 (84.7)
	Once daily pill	32 (9.1)	28 (7.9)	35 (9.9)	37 (10.5)
	Both are equal	35 (9.9)	47 (13.3)	25 (7.1)	17 (4.8)
Prevention					
Male (80)	Once a year i.v.	62 (77.5)	58 (72.5)	66 (82.5)	63 (78.8)
	Once daily pill	6 (7.5)	6 (7.5)	8 (10.0)	9 (11.3)
	Both are equal	12 (15.0)	16 (20.0)	6 (7.5)	8 (10.0)
Female (189)	Once a year i.v.	155 (82.0)	150 (79.4)	163 (86.2)	160 (84.7)
	Once daily pill	18 (9.5)	15 (7.9)	15 (7.9)	18 (9.5)
	Both are equal	16 (8.5)	24 (12.7)	11 (5.8)	11 (5.8)
Treatment					
Post-menopausal (227)	Once a year i.v.	177 (78.0)	172 (75.8)	183 (80.6)	187 (82.4)
	Once daily pill	24 (10.6)	20 (8.8)	26 (11.5)	28 (12.3)
	Both are equal	26 (11.5)	35 (15.4)	18 (7.9)	12 (5.3)
Pre-menopausal (126)	Once a year i.v.	109 (86.5)	106 (84.1)	110 (87.3)	112 (88.9)
	Once daily pill	8 (6.3)	8 (6.3)	9 (7.1)	9 (7.1)
	Both are equal	9 (7.1)	12 (9.5)	7 (5.6)	5 (4.0)
Prevention					
Post-menopausal (131)	Once a year i.v.	102 (77.9)	101 (77.1)	109 (83.2)	107 (81.7)
	Once daily pill	16 (12.2)	12 (9.2)	13 (9.9)	16 (12.2)
	Both are equal	13 (9.9)	18 (13.7)	9 (6.9)	8 (6.1)
Pre-menopausal (58)	Once a year i.v.	53 (91.4)	49 (84.5)	54 (93.1)	53 (91.4)
	Once daily pill	2 (3.4)	3 (5.2)	2 (3.4)	2 (3.4)
	Both are equal	3 (5.2)	6 (10.3)	2 (3.4)	3 (5.2)

10, regardless of subgroup. These early changes in BTMs may be useful in assessing response to ZOL therapy in patients with GIO. The authors have previously published results of a study that showed that ZOL increased lumbar spine BMD, measured by dual-energy X-ray absorptiometry, in both prevention and treatment subgroups. A single once-yearly 5 mg i.v. infusion of ZOL was non-inferior and possibly more effective than daily 5 mg oral RIS for the prevention and treatment of bone loss associated with GC use [28]. BMD measurement alone is not considered to be sensitive enough to assess bone strength; however, measurement of biochemical markers of bone turnover can be a useful tool to assist in the assessment of treatment response in patients with GIO who are on anti-resorptive therapy. Several earlier studies have reported that increases in BTM levels correlate with BMD loss at some skeletal sites and were predictive of fracture risk [35–41]. Anti-resorptive therapies, such as bisphosphonates, have been used to reduce the risk of osteoporotic vertebral, hip and other non-vertebral fractures, to maintain or improve bone mass and to suppress excessive bone turnover. However, in this study the number of subjects with clinical fractures or new morphometric vertebral fractures in the overall study population was too small to assess whether the reduction in biochemical markers of bone turnover correlate to a clinically meaningful reduction in fracture risk. Earlier studies have demonstrated that a once-yearly 5 mg i.v. infusion of ZOL is effective in preventing fractures in other osteoporotic subpopulations [20, 42, 43]. Hence we speculate that an annual infusion of 5 mg of ZOL may be efficacious in preventing fractures in different patient subgroups with GIO.

As previously published, this study has shown that ZOL has a good safety and tolerability profile [28]. The strength of this *post hoc* analysis is its large population size, where subjects were stratified into prevention and treatment subpopulations based on prior GC therapy and gender, which provided a meaningful basis for analyses by menopausal status. Hence the present study could identify the effects of anti-resorptive therapy in subgroups of patients with GIO. The study limitation with respect to BTM is that it was of short duration (12 months) and was not designed to assess BTM endpoints for the primary efficacy objective. There were insufficient numbers of clinical vertebral fractures and morphometric

vertebral fractures to assess the relationship between changes in bone markers and fracture risk reduction in patients with GIO. Patient preference for once-yearly i.v. infusion of ZOL over oral bisphosphonate was in agreement with previous studies [44, 45]. This may be attributed to the convenience associated with the once-yearly frequency of ZOL administration compared with daily oral RIS, leading to better compliance and hence contributing to better efficacy.

Overall, ZOL was found to be an effective and well-tolerated bisphosphonate in the management of patients with GIO. The rapid and sustained reductions of BTMs after ZOL administration were replicated across multiple subgroups of patients with GIO, including men and pre- and post-menopausal women, and were independent of GC doses.

Conclusions

In conclusion, a single 5 mg i.v. infusion of ZOL induced a significant and sustained reduction in biochemical markers of bone turnover, regardless of baseline characteristics such as gender, menopausal status and prednisone-equivalent GC dose. A rapid decrease in β-CTx was observed within days of ZOL administration, followed by a slow increase over the course of the year, suggesting that in patients on high-dose GC and with underlying inflammatory processes, bone turnover remains active despite potent anti-resorptive therapy. Further studies to assess the impact of BTM reduction on osteoporotic fractures in different subgroups of patients with GIO are warranted.

Rheumatology key messages

- Patients with glucocorticoid-induced osteoporosis undergo rapid bone loss early after treatment initiation.
- Treatment with bisphosphonates rapidly decreases the bone resorption marker β-CTx in patients with glucocorticoid-induced osteoporosis.

Acknowledgements

We acknowledge the contributions of the trial steering committee who designed the study. J.-P.D., P.S. and J.-Y.R. were members of the trial steering committee, recruited patients and helped edit the report. D.M.R. recruited patients, chaired the trial steering committee, wrote the outline of the report and completed editing of the final version. J.-Y.R., S.G., S.I.-S. and J.C. analysed and interpreted bone turnover markers data. P.P. and C.B.-R. participated in design of the study protocol, management of the trial and analysis and interpretation of the data in collaboration with all committee members. G.S. performed statistical analysis and interpretation of data. All the authors have critically reviewed the manuscript and approved the final version. We thank all the participants and research staffs in this multicentre study. We acknowledge writing support from Rajeeb Ghosh and editorial support from Ashutosh Kumar, Gowry Das and Ganesh Sangle, Novartis Healthcare Pvt. Ltd in the preparation of this manuscript. This article is dedicated to the memory of Professor Philip Sambrook (1952–2012), who passed away during the preparation of this manuscript. He had been very active in the field of glucocorticoid-induced osteoporosis and particularly in this study.

Funding: The study was financially supported by Novartis Pharma AG.

Disclosure statement: C.B.-R. is an employee of Novartis and owns stock or stock options in Novartis. S.G. has received research grant support from Novartis and Warner Chillcott, serves as a clinical trial investigator for Amgen, Eli Lilly, Merck, Sharp & Dohme, Novartis, Procter & Gamble and Servier & Wyeth Research; he has received consulting and speaker fees from Daichii Sankyo, Eli Lilly, Merck, Shape & Dome, Novartis, Warner Chillcott and Servier. G.S. is an employee of Novartis and owns stock or stock options in Novartis. D.M.R. is a consultant for, on the advisory board and/or received lecture fees from Pfizer, Novartis, Roche, Amgen, GlaxoSmithKline and AstraZeneca; and grant support from Roche, Novartis and TMRI Scotland and has equity ownership or stock options in AstraZeneca and GlaxoSmithKline. J.-P.D. has received consulting or advisory board fees from Novartis; lecture fees from Merck, Sharpe & Dohme, Procter & Gamble, Servier and Roche; and grant support from Schering-Plough, Abbott, Amgen, Novartis, Servier, Merck, Sharpe & Dohme, Procter & Gamble and Fonds National de Recherche Scientifique Medicale Belge. J.-Y.R. has received consulting, advisory board and/or lecture fees from Servier, Novartis, Negma, Eli Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS, Thermamex, Nycomed and Novo Nordisk; grant support from Bristol Myers Squibb, Merck, Sharpe & Dohme, Rottapharm, Teva, Eli Lilly, Novartis, Roche, GlaxoSmithKline, Amgen and Servier; and speaker fees from Merck, Sharp & Dohme, Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKline, Teijin, Teva, Ebewee Pharma, Zodiac, Analis, Theramex, Nycomed, Novo-Nordisk and Nolver. P.P. is an employee of Novartis and owns stock or stock options in Novartis. S.I.-S. has received research grants and consulting, advisory board and/or lecture fees from Merck, Sharp & Dohme, Eli Lilly, Transpharma, GlaxoSmithKline and Novartis. P.S. has received consulting or advisory board fees from Merck, Sanofi Aventis, Servier and Novartis; lecture fees from Roche; and grant support from the Australian National Health and Medical Research Council. The other author has declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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