Bone 50 (2012) 289–295

Contents lists available at SciVerse ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

Bisphosphonates and glucocorticoid osteoporosis in men: results of a randomized controlled trial comparing zoledronic acid with risedronate☆,☆☆

Philip N. Sambrook [a,*], Christian Roux [b], Jean-Pierre Devogelaer [c], Kenneth Saag [d], Chak-Sing Lau [e], Jean-Yves Reginster [f], Christina Bucci-Rechtweg [g], Guoqin Su [g], David M. Reid [h]

[a] University of Sydney, Sydney, NSW, Australia
[b] Paris-Descartes University, Paris, France
[c] Université Catholique de Louvain at Brussels, Brussels, Belgium
[d] University of Alabama at Birmingham, Birmingham, AL, USA
[e] University of Dundee, Dundee, UK
[f] University of Liège, Liège, Belgium
[g] Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
[h] University of Aberdeen, Aberdeen, UK

ARTICLE INFO

Article history:
Received 22 June 2011
Revised 15 September 2011
Accepted 24 October 2011
Available online 29 October 2011

Edited by: David Fyhrie

Keywords:
Glucocorticoids
Osteoporosis
Zoledronic acid
Risedronate
Bone mineral density

ABSTRACT

Background: We studied 265 men (mean age 56.4 years; range 18–83 years), among patients enrolled in two arms of a double-blind, 1-year study comparing the effects of zoledronic acid (ZOL) with risedronate (RIS) in patients either commencing (prednisolone 7.5 mg/day or equivalent) (prevention arm, n = 88) or continuing glucocorticoid therapy (treatment arm, n = 177).
Methods: Patients received either a single ZOL 5 mg infusion or RIS 5 mg oral daily at randomization, along with calcium (1000 mg) and vitamin D (400–1200 IU). Primary endpoint: difference in percentage change from baseline in bone mineral density (BMD) at the lumbar spine (LS) at 12 months. Secondary endpoints: percentage changes in BMD at total hip (TH) and femoral neck (FN), relative changes in bone turnover markers (β-CTx and P1NP), and overall safety.
Findings: In the treatment subpopulation, ZOL increased LS BMD by 4.7% *vs.* 3.3% for RIS and at TH the percentage changes were 1.8% *vs.* 0.2%, respectively. In the prevention subpopulation, bone loss was prevented by both treatments. At LS the percentage changes were 2.5% *vs.* −0.2% for ZOL *vs.* RIS and at TH the percentage changes were 1.1% *vs.* −0.4%, respectively. ZOL significantly increased lumbar spine BMD more than RIS at Month 12 in both the prevention population ($p = 0.0024$) and the treatment subpopulation ($p = 0.0232$) in men. In the treatment subpopulation, ZOL demonstrated a significantly greater reduction in serum β-CTx and P1NP relative to RIS at all time-points. In the prevention subpopulation, ZOL significantly reduced β-CTx at all time-points, and P1NP at Month 3 ($p = 0.0297$) only. Both treatments were well tolerated in men, albeit with a higher incidence of influenza-like illness and pyrexia events post-infusion with ZOL.
Interpretation: Once-yearly ZOL preserves or increases BMD within 1 year to a greater extent than daily RIS in men receiving glucocorticoid therapy.

Introduction

Glucocorticoids are used widely for their anti-inflammatory and immunosuppressive properties in the treatment of a wide variety of diseases including pulmonary, gastrointestinal and autoimmune disorders, as well as in organ transplantation and oncology. The use of glucocorticoids is, however, often associated with adverse effects, even with careful and vigilant use [1–5]. Glucocorticoid-induced osteoporosis (GIO) is the leading cause of medication-induced osteoporosis and one of the most problematic complications of persistent use of glucocorticoid therapy. GIO is associated with rapid bone loss and increased risk of fragility fractures especially within the first few months after initiation of the therapy even when used at low doses [1–3,6–11].

Abbreviations: ZOL, Zoledronic Acid; RIS, Risedronate; BMD, Bone Mineral Density; LS, Lumbar Spine; TH, Total Hip; FN, Femoral Neck; GIO, Glucocorticoid-induced Osteoporosis; HORIZON, Health Outcomes and Reduced Incidence with zoledronic Acid ONce yearly; P1NP, Procollagen type 1 Aminoterminal Propeptide; β-CTx, β-C-terminal Telopeptides of type 1 collagen.

☆ Funding Research sponsored by Novartis Pharma AG, Basel, Switzerland.
☆☆ This trial is registered with ClinicalTrials.gov, number NCT00100620.

* Corresponding author at: Department of Rheumatology, Kolling Institute of Medical Research (Bone & Joint Research), Sydney Medical School, Royal North Shore Hospital, St. Leonards NSW 2065, Australia. Fax: +61 299061859.
E-mail address: sambrook@med.usyd.edu.au (P.N. Sambrook).

8756-3282/$ – see front matter © 2011 Published by Elsevier Inc.
doi:10.1016/j.bone.2011.10.024

Early intervention with bone-sparing pharmacological agents is indicated for preventing bone loss and reducing fracture risk in patients receiving glucocorticoid therapy based on the dose and expected duration of glucocorticoid treatment, age and sex of the patient and baseline bone mineral density (BMD) at the start of the therapy [2,12–15].

Bisphosphonates, structural analogs of inorganic pyrophosphate, are recommended as the first-line treatment for the prevention and treatment of GIO by several international guidelines due to their anti-resorptive effects [4,10,11,13,16,17]. The mechanisms by which bisphosphonates reduce the adverse skeletal effects of glucocorticoids have not been fully elucidated. Bisphosphonates induce osteoclast apoptosis, thereby decreasing bone resorption and reducing the rate of bone remodeling. Additionally, bisphosphonates prevent osteoblast and osteocyte apoptosis *in vivo* and *in vitro* by a distinct mechanism leading to a gradual increase in trabecular thickness [13,14,18,19].

In several clinical trials, bisphosphonates have been found to be effective in increasing BMD and reducing the incidence of vertebral fractures in patients initiating or continuing glucocorticoid therapy [20–29]. However, most of the trials on GIO have largely studied postmenopausal women, with only small proportions of men [5,9,12,15,21,25,26,30,31]. Only risedronate trials in GIO separately reported results in men [22,32], but few other studies have had large enough populations of men to warrant separate reporting. Some of the mechanisms of glucocorticoid-induced bone loss appear to be independent of a patient's sex, but not all, so that separate reporting of men data in larger studies is of interest. For example baseline bone turnover, circulating sex steroids and absolute BMD values all differ between genders [17,33,34].

The Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly (HORIZON) trial for the prevention and treatment of GIO [35] reported that a single intravenous (i.v.) infusion of zoledronic acid (ZOL) 5 mg was associated with a greater increase in BMD and a more rapid and substantial decreases in bone turnover than daily oral risedronate (RIS) 5 mg in patients initiating or continuing on long-term glucocorticoid therapy. Because most trials in GIO have recruited a majority of postmenopausal women, a common clinical question in GIO is whether the therapy trialed works in subgroups such as in men or premenopausal women. Because we recruited a large number of men in absolute terms in this trial, this report deals with this subgroup in detail not addressed in the major report of this study [35].

Methods

Study design

In this multinational, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group study patients initiating or continuing on high-dose glucocorticoid therapy (≥7.5 mg/day of prednisolone or equivalent) were randomized (1:1) to receive a single ZOL 5 mg i.v. infusion or oral RIS 5 mg for 1 year. Patients were stratified into two subpopulations based on the duration of glucocorticoid therapy at baseline: the “prevention” subpopulation (patients using high-dose glucocorticoid therapy for ≤3 months or less) and the “treatment” subpopulation (patients using high-dose glucocorticoid therapy for >3 months). All patients also received supplemental calcium (1000 mg) and vitamin D (400–1200 IU) daily throughout the study [35].

Participants

Male patients aged 18–85 years, requiring high-doses of glucocorticoid therapy due to some underlying clinical conditions, and expected to continue the therapy for a minimum of 1 year were included in this sub-study report. Patients were enrolled at community hospitals and clinics from 54 centers in 16 countries (Australia, Belgium, Czech Republic, Estonia, Finland, France, Hong Kong, Hungary, Israel, Lithuania, Poland, Romania, Spain, Switzerland, UK, and USA). Patients were selected from two cohorts based on duration of the glucocorticoid therapy at the time of enrollment (≤3 months or >3 months). Radiography of the lumbar spine was done to ensure the accessibility of at least three evaluable lumbar vertebrae (L1 to L4 region) for measuring BMD [35].

Major exclusion criteria were prior treatment with bisphosphonates or other drugs that may affect bone mineral metabolism (except in accordance with a predefined washout schedule), serum 25-hydroxyvitamin D concentration<30 nmol/L, recent history of cancer or parathyroid disease, and renal impairment (creatinine clearance<30 mL/min or proteinuria) [35].

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki (1989) and local applicable laws and regulations. Approval was obtained from an Institutional Review Board or Independent Ethics Committee or Research Ethics Board for each participating study center before the start of the study. All patients provided written informed consent prior to participating in the study. Clinical Trial Registration Number: NCT00100620.

Assessments

Efficacy assessments

In this study, the primary endpoint for drug efficacy was the percentage change from baseline in BMD of the lumbar spine (L1–L4) at 12 months. The secondary endpoints included the percentage change from baseline in BMD at other sites (total hip and femoral neck) and relative changes in biochemical markers of bone turnover (β-C-terminal telopeptides of type 1 collagen [β-CTx] and procollagen type 1 aminoterminal propeptide [P1NP]) at 12 months [35].

BMD of the lumbar spine, total hip and femoral neck was measured by dual-energy X-ray absorptiometry at screening, Month 6 and Month 12 in each center, analyzed at a central laboratory, BioImaging Technologies BV, Leiden, The Netherlands, and the percentage change from baseline was calculated in the prevention and the treatment subpopulation. Markers of bone resorption (β-CTx) and bone formation (P1NP) were measured at baseline, 9–11 days, 3, 6 and 12 months using specific serum tests at Supreme/Bone and Cartilage Markers Laboratory at the University of Liège (Liège, Belgium) and the relative changes from baseline were assessed [35]. Morphometric vertebral fractures were assessed using the semiquantitative method of Genant et al. [36].

Safety assessments

Safety assessments included adverse events and serious adverse events with their severity and relationship to the study drug as assessed by the investigators. Independently, blinded expert committees adjudicated all laboratory investigations (hematology, blood chemistry and urine) and targeted adverse events (ocular events, osteonecrosis of the jaw, avascular necrosis at other skeletal sites, cardiac arrhythmias, deteriorating renal function, hypocalcaemia, delayed fracture healing, and primary cause of death) [35].

Statistical analysis

Demography and baseline characteristics were summarized for the intention-to-treat (ITT) population (which consisted of all patients randomized to treatment) and the modified ITT population (which consisted of randomized patients having baseline and at least one post-baseline measurement). A daily prednisolone-equivalent dose of glucocorticoid therapy was calculated to standardize the different glucocorticoid treatments used by patients in the study, considering only the medications taken orally. As the magnitude of effect of RIS on percentage change in BMD differs for GIO treatment and