Bone 49 (2011) 82–88

Contents lists available at ScienceDirect

Bone

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

Review

Bisphosphonates for postmenopausal osteoporosis ☆

Richard Eastell [a,*], Jennifer S. Walsh [a], Nelson B. Watts [b], Ethel Siris [c]

[a] National Institute for Health Research Biomedical Research Unit for Bone Disease, Centre for Biomedical Research, Northern General Hospital, Herries Road, Sheffield, South Yorkshire, S5 7AU, England, UK
[b] University of Cincinnati Bone Health and Osteoporosis Center, Cincinnati, OH, USA
[c] Toni Stabile Osteoporosis Center, Department of Medicine, Columbia University Medical Center, New York, NY, USA

ARTICLE INFO

Article history:
Received 27 November 2010
Revised 24 January 2011
Accepted 14 February 2011
Available online 22 February 2011

Edited by: David Burr

Keywords:
Osteoporosis
Alendronate
Ibandronate
Clodronate
Zoledronic acid
Risedronate

ABSTRACT

Bisphosphonates are effective in reducing bone turnover, increasing BMD and reducing fracture risk in postmenopausal women with osteoporosis. The licensed bisphosphonates exhibit some differences in potency and speed of onset and offset of action. These differences mean that different agents may be more advantageous in different situations.

Uncertainties still exist around the optimum duration of treatment and treatment holidays, how best to use bisphosphonates with anabolic treatments, and the benefits of treatment in patients who do not have a BMD T-score below −2.5.

This article is part of a Special Issue entitled Bisphosphonates.

Contents

Introduction

The earliest reported use of bisphosphonate treatment for postmenopausal osteoporosis was in 1976 [1] when oral etidronate was administered to 10 women with osteoporosis and the authors noted a significant improvement in calcium balance. It was a further 15 years until oral etidronate (given at a much lower dose and in a cyclical regime) was licensed in countries including the UK (although it was never licensed for use in the USA).

☆ Supported by the National Institute for Health Research National Institute for Health Research (NIHR) via its Biomedical Research Units Funding Scheme. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

* Corresponding author at: NIHR Bone Biomedical Research Unit, Centre for Biomedical Research, Northern General Hospital, Herries Road, Sheffield, South Yorkshire, S5 7AU, England, UK. Fax: +44 114 261 8775.
E-mail address: r.eastell@sheffield.ac.uk (R. Eastell).

8756-3282/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.bone.2011.02.011

Subsequently, a number of bisphosphonates have been evaluated in postmenopausal osteoporosis and investigated in large clinical trials with fracture as an end-point. This has resulted in the licensing of alendronate, risedronate, ibandronate and zoledronic acid for the treatment of postmenopausal osteoporosis (Table 1).

The purpose of this article is to consider the evidence that bisphosphonates reverse the key pathophysiological changes of postmenopausal osteoporosis, to compare the efficacy of each of the licensed bisphosphonates based on clinical trial data and address key questions that have arisen from these trials about the efficacy of different bisphosphonates. Drug safety and the use of bisphosphonates in other clinical settings will be covered in other articles in this issue. In general, the bisphosphonates are well tolerated. Patients may develop abdominal pain or dyspepsia that occurs within hours of taking the oral bisphosphonate and that is relieved by stopping the medication. Patients may develop an influenza-like illness within a few days of receiving an intravenous injection of an amino bisphosphonate (such as zoledronic acid) and this is usually worse after the first such injection rather than subsequent injections. These issues may limit the acceptance of the medication.

Pathogenesis

Bone loss occurs in postmenopausal osteoporosis as a result of an increase in the rate of bone remodeling and an imbalance between the activity of osteoclasts and osteoblasts [2]. Bone remodeling occurs at discrete sites within the skeleton and proceeds in an orderly fashion with bone resorption always being followed by bone formation, a phenomenon referred to as 'coupling'. The sequence of bone remodeling is similar in both cortical and cancellous bone [3]. The quiescent bone surface is converted to activity ('origination') and the osteoclasts resorb bone ('progression') forming either a cutting cone (cortical bone) or a trench (cancellous bone). Osteoblasts then synthesize bone matrix that subsequently becomes mineralized. The sequence takes up to eight months. A remodeling imbalance results when the processes of bone resorption and bone formation are not matched. In postmenopausal women, as well as in a variety of other circumstances, this imbalance is magnified by the increase in the rate of initiation of new bone remodeling cycles ('activation frequency'). In women with postmenopausal osteoporosis, there is a greater increase in activation frequency (number of remodeling events) and the duration of the remodeling cycle may be longer than in young women.

Remodeling imbalance manifests in ways that affect the structure of bone. One is the accumulation of large Haversian spaces in cortical bone, [4] leading to increased cortical porosity [5]. The other involves perforation and loss of the normal trabecular microarchitecture as osteoclasts penetrate the trabecular plates. These examples demonstrate how random remodeling errors tend to reduce cancellous and cortical bone density and compromise structural integrity.

Table 1
Key dates in the development of bisphosphonates for postmenopausal osteoporosis.

Bisphosphonate	US license date for osteoporosis	First study	Key fracture study
Etidronate (cyclic, oral)	No	Anderson 1984 [47]	Storm 1990 [48] Watts 1990 [49]
Clodronate (oral)	No	Kanis 1996 [50]	McCloskey 2007 [51]
Tiludronate (cyclic, oral)	No	Reginster 1989 [52]	Reginster 2001 [53]
Pamidronate (i.v.)	No	Peretz 1996 [54]	None
Alendronate	1995	Harris 1993 [55]	Liberman 1995 [18] Black 1996 [20] Cummings 1998 [19]
Risedronate	1998	Mortensen 1998 [56]	Harris 1999 [57] Reginster 2000 [58] McClung 2001 [42]
Ibandronate	2003	Thiebaud 1997 [17]	Chesnut 2004 [59]
Zoledronic acid	2007	Reid 2002 [16]	Black 2007 [31] Lyles 2007 [60]

US license dates from FDA website, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails.

The effects of bisphosphonates on activation frequency and remodeling imbalance have been evaluated in clinical trials. Bisphosphonates reduce the activation frequency of new remodeling units (Fig. 1). Alendronate has been observed to have the greatest and risedronate the smallest effect; however, this comparison was between the treatment and placebo groups after three years of treatment at the licensed dose (alendronate 10 mg/day, risedronate 5 mg/day, ibandronate 2.5 mg/day oral or 3 mg/3 months i.v. or zoledronic acid 5 mg i.v. per year) and not the change from baseline. This information was only available for risedronate. Furthermore, bone biopsies from patients taking zoledronic acid in these studies, were taken close to the end of the treatment period and so may underestimate changes in bone turnover shortly after the infusion.

Is there evidence for less negative remodeling balance with bisphosphonates? Bone balance was reported in two studies. These showed that there was no effect of bisphosphonate therapy on bone balance over three years when the drug was given at the licensed dose for either alendronate [6] or risedronate [7] compared to placebo.

Mean wall thickness was only reported in two studies. These studies showed that there was no effect of bisphosphonate therapy on mean wall thickness over three years at the licensed dose for zoledronic acid [8] or ibandronate [9] compared to placebo. Thus, there is evidence of restoration (or reduction) of activation frequency from the clinical trials but no evidence of restoration of remodeling imbalance. Thus, bone turnover is decreased, but remodeling imbalance is not affected by bisphosphonate therapy; this decrease slows the structural decay of bone.

Efficacy

Bone turnover markers

Bone turnover marker response to bisphosphonates has been studied. In general, there is an early decrease (2–4 weeks) in bone resorption markers and a later decrease (3–6 months) in bone formation markers. The effect of some bisphosphonates on bone resorption markers is earlier than others, for example, zoledronic acid has more rapid effects than alendronate [10] (Fig. 2). This quicker effect is likely to

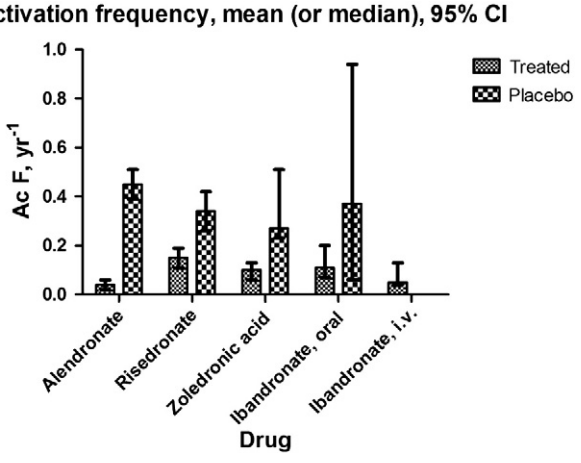

Fig. 1. Effect of 3-yr of bisphosphonate therapy on activation frequency in the placebo and active arms (at the licensed dose) of trials with alendronate 10 mg/day [6], risedronate 5 mg/day [7], zoledronic acid 5 mg/year [8] and oral (2.5 mg/day) or intravenous (3 mg/3 month) ibandronate [9]. The results displayed are the means (or median in the case of zoledronic acid and ibandronate) and 95% (or 90% for ibandronate) confidence interval. For ibandronate, the placebo group was replaced by a referent population.