Naranjo A[1], Ojeda S[1], Hernández-Beriaín JA[2], Talaverano S[3], Nóvoa-Medina J[2], Álvarez F[4] y grupo ToARCan

1 Hospital Universitario de Gran Canaria Dr. Negrín

2 Complejo Hospitalario Universitario Materno Insular de Gran Canaria

3 Hospital Dr. Molina Orosa - Lanzarote

4 Hospital Universitario Ntra. Sra. de la Candelaria - Tenerife

Use of bisphosphonates in postmenopausal women with rheumatoid arthritis; results of a multicentre study

Correspondence: Antonio Naranjo - c/Barranco de la Ballena, s/n - 35010 Las Palmas de Gran Canaria - Las Palmas (Spain)
e-mail: anarher@gobiernodecanarias.org

Date of receipt: 13/04/2015
Date of acceptance: 11/06/2015

Summary

Objective: The objective of this study was to analyse the use of bisphosphonates in women with rheumatoid arthritis (RA) in the Canary Islands.

Material and methods: This multicentre observational study included women aged 50 years or over. At a single visit, demographic variables and those relating to the RA, history of fragility fractures, use of corticoids, performance of bone densitometry (DXA) and current treatment with bisphosphonates were recorded. The simplified FRAX ® tool was used and the recommendations of the American College of Rheumatology (ACR) for the prophylaxis of osteoporosis with corticoids were applied.

Results: 192 women were included, with an average age of 62 years. A total of 91 (48%) patients were receiving corticoids; 17 of these (9%) had suffered a fracture; 123 (66%) had had a DXA; and 52 (28%) were taking bisphosphonates (70% of the patients with osteoporosis or fracture and 45% of those with criteria for prophylactic use of corticoids for osteoporosis). Those factors having a significant association with the use of bisphosphonates were age, duration of the disease, the HAQ functional capacity questionnaire, the risk of fracture determined by FRAX®, treatment with corticoids, history of fracture and the previous performance of DXA. In the multivariate study only the DXA (p=0.03) and history of fracture (p=0.02) were significantly associated.

Conclusions: In postmenopausal women from the Canary Islands with RA the prescription of bisphosphonates could conform better to the guidelines, especially in patients receiving treatment with corticoids.

Key words: *rheumatoid arthritis, osteoporosis, fracture, bisphosphonates, bone densitometry.*

Introduction

Patients with rheumatoid arthritis (RA) have an increased risk of osteoporosis (OP) and of fracture. The prevalence of osteoporosis in RA is between 17% and 32% in the spine and between 15% and 36% in the hip[1,2]. In addition to the classic risk factors, the disease itself and the use of corticoids are considered as independent factors for the risk of fracture, as is outlined in the FRAX® tool[3]. In the clinical monitoring of the patient with RA, the rheumatologist takes into account the guides to the management of OP[4,5], as well as the guides to the prevention of corticoid-induced osteoporosis[6,7].

This study analyses the use of bisphosphonates in postmenopausal women with RA in clinical practice.

Material and methods

A multicentre observational study was carried out in five hospitals in the Canary Islands (four university hospitals and one district hospital), which included consecutive patients attending the rheumatology clinic. The study was approved by the ethics committee for clinical research of the University of Gran Canaria Dr Negrin Hospital, and the patients gave their written consent. The inclusion criteria were: women of 50 or more years of age attending a clinic with a diagnosis of RA (1997 and/or 2010 criteria). The exclusion criterion was that the arthritis had been developing for less than 6 months.

The collection of the data was carried out in a single visit by the doctor who regularly treated the patient. Thus, the data collected were the following: age of the patient, sex, period of development of the disease, presence/absence of rheumatoid factor, extra-articular manifestations, erosive disease, performance of a DXA, history of fragility fracture after the age of 50, the taking of corticoids, duration and dose, and treatment with bisphosphonates. Also collected in that visit were disease-modifying (DMDs)) and biological treatments. The patient completed the questionnaire on functional capacity – the Health Assessment Questionnaire (HAQ)[8]. The risk of fracture was quantified using a simplified FRAX® index using age, sex, smoking habit, history of fragility fracture after the age of 50, RA and the use of corticoids. The reason for using the simplified FRAX® index was the non-availability of all the necessary data, such as family history of hip fracture in forebears, alcohol consumption or early menopause. A weight and height of 60 kg and 160 cm, respectively, were established to obtain a BMI of 23.4 for all the patients.

The percentage of patients treated with bisphosphonates was analysed and the ACR criteria for the prophylaxis of corticoid-induced osteoporosis were applied[7]. In short, all postmenopausal women or those over 50 years of age with RA and corticoids are candidates for bisphosphonates, except those who have a risk of major fracture according to FRAX® of less than 10%, as well as a dose of less than 7.5 mg/d of prednisone, and who neither present osteoporosis by DXA, nor history of fragility fracture.

A descriptive statistical analysis was performed with parametric and non-parametric tests for comparison of groups. The differences between hospitals were analysed using Fisher's exact test. To analyse the factors associated with the use of bisphosphonates a multiple regression multivariate model was used with thoseparameters with statistical significance in the bivariate analysis. SPSS (Statistical Package for Social Sciences version 15.0) was used and the statistical significance was placed at $p<0.5$.

Results

The fieldwork was carried out between March 2013 and March 2014. 192 women were included, whose characteristics are set out in Table 1.

At their visit, 48% of the patients were receiving corticoids, with an average dose of 6 mg of prednisone (standard deviation – SD - 2.8 mg): 27% of the total were taking ≥5 mg for at least 3 months.

The average risk of fracture, measured by FRAX® in 185 patients was 8.2±7.3% for a major fracture and 3.55% for a hip fracture. In 149 patients (77%), the risk of major fracture was less than 10%, in 23 patients (12%) it was between 10% and 20%, while in 20 patients (10%) it was above 20%. The risk of hip fracture was higher than 3% in 46 patients (24%).

A DXA had been performed on 66% of the patients with a range according to hospital from 36% to 87% ($p<0.001$), the results being osteoporosis in 26%, low bone mass in 49% and normal in 24%. In comparison with those patients who had not had a DXA, the patients who had had the test more commonly had a risk of fracture >20% (3% vs 12%: $p=0.04$).

At the current visit 28% were receiving bisphosphonates, with a range of 14% to 39% depending on the hospital ($p=0.09$). Table 2 shows the patients in treatment with or without bisphosphonates, and the associated factors.

33 of the of the 88 patients (37%) in treatment with corticoids were taking bisphosphonates. 44 patients met the ACR criteria for OP prophylaxis, of whom 20 (45%) were taking bisphosphonates. 21 of the 30 cases (70%) with osteoporosis according to the DXA, and 12 of the 17 cases with a previous fracture (70%) were receiving bisphosphonates. In nine patients more than one of these conditions applied.

A significant association was observed between treatment with bisphosphonates and age, the duration of the disease, the average incapacity according to the HAQ, the average risk of fracture according to FRAX®, history of fragility fracture (OR 9.86; 95% CI: 9.26-10.47), treatment with corticoids (OR 2.49; 95% CI: 2.15-2.83) and the performance of a DXA (OR 9.59; 95% CI: 9.04-10.14) (Table 2). In the multivariate study, in which the variable dependent was the use of bisphosphonates, only the DXA ($p=0.03$) and history of fracture ($p=0.02$) were significant.

Discussion

The multicentre study which we present is a snapshot from real clinical practice of the approach to osteoporosis in patients with RA being monitored by a rheumatologist. A significant difference is observed in the request for DXA between the different hospitals, there being a less marked difference in the use of bisphosphonates. The ordering of a DXA is more frequent in patients at higher risk of fracture, a fact reported in a study of Japanese women with RA[9]. The use of bisphosphonates in our study was associated with the carrying out of a DXA and with history of fracture, but not with the risk determined by FRAX®, or with the use of corticoids after the multivariate study. Thus, slightly less than half of the patients with criteria for the prophylaxis of osteoporosis by corticoids were taking bisphosphonates, a similar figure to that reported in a North American study[10]. The guide of the Spanish Society of Internal Medicine recommends prophylactic treatment for corticoid-induced osteoporosis in postmenopausal women if they are going to receive, or are receiving, >5 mg/day of prednisone or equivalent for more than 3 months[6]. On their part, the consensus of the Spanish Rheumatology Society advises preventative measures in those patients who are going to take doses equivalent to ≥5 mg/day of prednisone for more than 3 months, reserving pharmacological treatment for those patients with a risk factor[4]. Neither consensus is specific to patients with RA.

In the CANAL study, which included female postmenopausal primary care patients with an average age of 63 years referred for DXA, the average FRAX® for major fracture was 6.1% in the subgroup from the Canary Islands[11], while in this study with RA the average FRAX® was 8.2%. The percentage of women treated in the Canarian group of the CANAL study was 28%, exactly the same as the patients with RA in this study, in spite of the fact that the risk of fracture in RA is higher. The results of our work suggest that in the absence of DXA, the prescription of bisphosphonates in RA is not appropriate since neither the risk of fracture nor the taking of corticoids are evaluated as they should be. Two studies have analysed the prescription of treatment for osteoporosis in women of all ages with RA, varying between 22% and 32%[12,13]. A Japanese study of 3,970 patients with RA found that only 44% of those with a high risk had been prescribed bisphosphonates[9], a similar figure to that in the north American CORRONA study[13], as well as in our study, in which 50% of women with a FRAX® higher than 10% were receiving bisphosphonates.

This study had various limitations: not all the risk factors for fracture were recorded, such as hip fracture of their forebears, alcohol, low weight, early menopause or other causes of secondary osteoporosis. Furthermore, the risk of fracture calculated by FRAX® is a simplification of the original. It has also been reported that other, simpler, tools may predict the risk of fracture in a similar way to FRAX®[14]. In any case, this simplified tool may always err due to its underestimation of the risk of fracture. On the other hand, we consider important the fact that our study includes a significant sample of patients being seen in five hospitals in real clinical practice.

In conclusion, in those patients with RA over 50 years of age in the Canary Islands the prescription of bisphosphonates by rheumatologists shows areas of improvement, especially in the evaluation of risk of fracture and in the prophylaxis of corticoid-induced osteoporosis.

Acknowledgements: Carmen Alonso, for administrative tasks, and Teresa Guzman for logistical support.

Financing: This study has a scholarship Abbvie (ACA-SPAI-12-17). Abbvie has not participated in the drafting of the summary or the decision to return.

ToARCan group (treatment for rheumatoid arthritis target in the Canaries): Antonio Naranjo, Félix Francisco, Soledad Ojeda, Juan Carlos Quevedo, Carlos Rodríguez-Lozano, Laura Cáceres (Hospital Universitario de Gran Canaria Dr. Negrín); José Ángel Hernández-Beriaín, Javier Nóvoa-Medina, Sergio Machín, (Complejo Hospitalario Universitario Materno Insular de Gran Canaria); Sigrid Talaverano, José Adán Martín (Hospital Dr. Molina Orosa, Lanzarote); Esmeralda Delgado, Elisa Trujillo, Beatriz-Rodríguez Lozano, Lorena Expósito, María Vanesa Hernández (Hospital Universitario de Canarias, Tenerife); Fátima Álvarez, Laura Magdalena Armas (Hospital Universitario NS Candelaria, Tenerife).

Conflict of interest: The first author, in the name of the other co-authors, declares that there are no conflicts of interest.

Bibliography

1. Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis-results from 394 patients in the Oslo County Rheumatoid Arthritis Register. Arthritis Rheum 2000;43:522-30.
2. Sinigaglia L, Nervetti A, Mela Q, Bianchi G, Del Puente A, Di Munno O, et al. A multicenter cross sectional study on bone mineral density in rheumatoid arthritis. J Rheumatol 2000;27:2582-9.
3. Disponible en: http://www.shef.ac.uk/FRAX/tool.jsp [consultado 2 de septiembre de 2014].
4. Pérez Edo L, Alonso Ruiz A, Roig Vilaseca D, García Vadillo A, Guañabens Gay N, Peris P, et al. Actualización 2011 del consenso Sociedad Española de Reumatología de osteoporosis. Reumatol Clin 2011;76:357-79.
5. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2010. National Osteoporosis Foundation.
6. Sosa Henríquez M, Díaz Curiel M, Díez Pérez A, Gómez Alonso C, Gonzalez Macias J, Farrerons Minguella J, et al. Guía de prevención y tratamiento de la osteoporosis inducida por glucocorticoides de la Sociedad Española de Medicina Interna. Rev Clin Esp

Table 1. Characteristics of patients included. The data are expressed as n (%), unless indicated otherwise

		N valid
Average age, years: mean (SD)	62 (8)	192
Average duration of illness, age: mean (SD)	11 (8)	192
Positive rheumatoid factor	156 (81)	192
Erosive RA	97 (54)	178
HAQ: mean (SD)	0.96 (0.7)	188
Extra-articular manifestations (*)	31 (17)	182
Arthritis in remission for DAS28 (**)	72 (37)	172
Treatment with FAME (***)	179 (93)	192
Biological treatment	61 (31)	192
Treatment with corticosteroids	91 (48)	188
Current smokers	24 (12)	188
Fragility fracture after age 50	17 (9)	183
Performed bone densitometry	123 (66)	185
Treatment with bisphosphonates	52 (28)	186

(*) Pulmonary fibrosis or vasculitis or Sjögren syndrome or rheumatoid nodules.
(**) Disease activity index <2.6.
(***) Disease modifying drugs.

Table 2. Comparison of two groups of patients as a function of treatment with bisphosphonates

	Group bisphosphonate N=52	Group without bisphosphonates N=134	p
Age, mean (SD)	65.7 (8)	60.7 (7)	<0.001
Duration of disease, years, mean (SD)	14 (9)	10 (8)	0.02
Erosive RA, N (%)	35 (67)	65 (48)	0.06
HAQ, mean (SD)	1.23 (0.7)	0.84 (0.6)	0.001
FRAX® higher, average fracture (SD)	12.0 (9)	6.4 (6)	<0.001
FRAX® hip fracture, mean (SD)	5.9 (6)	2.4 (4)	<0.001
Treatment with corticosteroids, N (%)	33 (63)	55 (41)	0.04
Bone densitometry was performed, N (%)	48 (92)	74 (55)	<0.001
Fragility fracture, N (%)	12 (23)	4 (3)	<0.001

2008;208:33-45.
7. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Care Res 2010;62:1515-26.
8. Esteve-Vives J, Batlle-Gualda E, Reig A. Spanish version of the Health Assessment Questionnaire: reliability, validity and transcultural equivalency. Grupo para la Adaptación del HAQ a la Población Española. J Rheumatol 1993;20:2116-22.
9. Furuya T, Hosoi T, Saito S, Inoue E, Taniguchi A, Momohara S, et al. Fracture risk assessment and osteoporosis treatment disparities in 3,970 Japanese patients with rheumatoid arthritis. Clin Rheumatol 2011;30:1105-11.
10. Watt J, Thompson A, Le Riche N, Pope J. There is still a care gap in osteoporosis management for patients with rheumatoid arthritis. Joint Bone Spine 2014;81:347-51.
11. Naranjo A, Rosas J, Ojeda S, Salas E. Manejo de la osteoporosis en atención primaria antes y después del resultado de la densitometría; tratamiento instaurado versus tratamiento recomendado en los consensos (estudio CANAL). Reumatol Clin 2013;9:269-73.
12. Heberlein I, Demary W, Bloching H, Braun J, Buttgereit F, Dreher R, et al. Prophylaxis and treatment of osteoporosis in patients with rheumatoid arthritis (ORA study). Z Rheumatol 2011;70:793-8.
13. Coulson KA, Reed G, Gilliam BE, Kremer JM, Pepmueller PH. Factors influencing fracture risk, T score, and management of osteoporosis in patients with rheumatoid arthritis in the consortium of rheumatology researchers of north america (CORRONA) registry. J Clin Rheumatol 2009;15:155-60.
14. Rubin KH, Abrahamsen B, Friis-Holmberg T, Hjelmborg JV, Bech M, Hermann AP, et al. Comparison of different screening tools (FRAX®, OST, ORAI, OSIRIS, SCORE and age alone) to identify women with increased risk of fracture. A population-based prospective study. Bone 2013;56:16-22.