

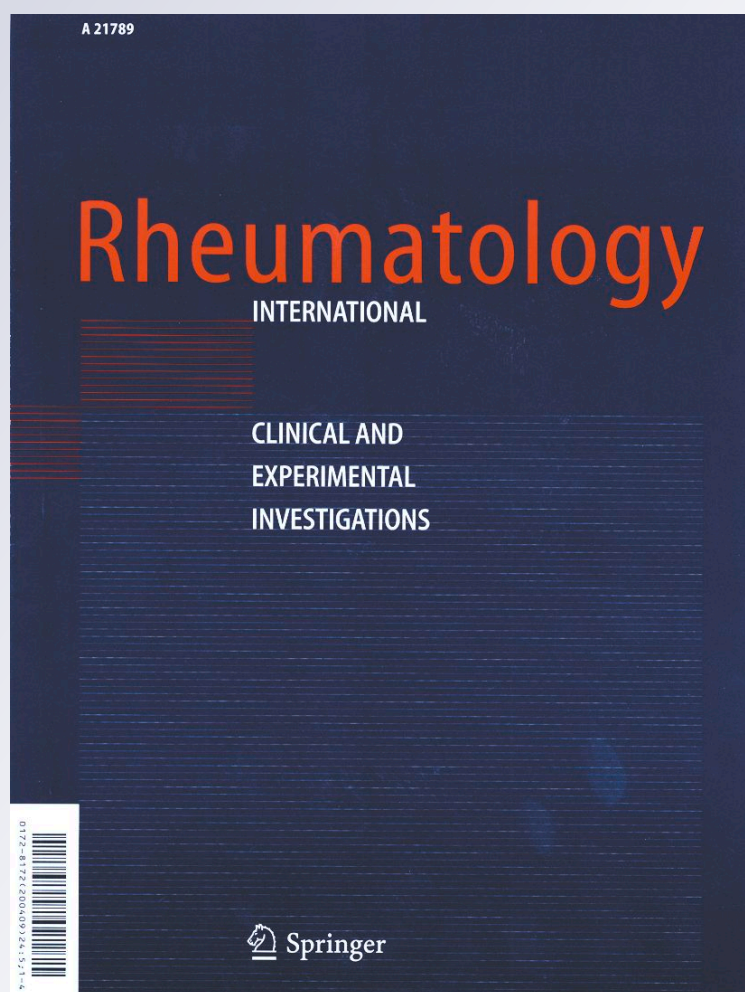
*Prescription for antiresorptive therapy
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strategies for osteoporosis prevention?*

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Prescription for antiresorptive therapy in Mexican patients with rheumatoid arthritis: is it time to reevaluate the strategies for osteoporosis prevention?

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Abstract Glucocorticoids are frequently used in rheumatoid arthritis (RA) in order to alleviate symptoms of joint inflammation, retard erosions and to treat extra-articular manifestations, although these drugs may increase the risk of bone mineral loss and osteoporotic fractures. To date, in Mexico there are no studies that identify the frequency of patients with RA with corticosteroids, receiving therapy for osteoporosis. Therefore, we evaluated the prevalence and factors related to the prescription of

antiresorptives in 520 Mexican patients with RA. We used a multivariate model to identify variables associated with antiresorptives prescription. We identified that although 79% of patients were under treatment with glucocorticoids, only 13% received antiresorptive agents as preventive therapy for osteoporosis. The multivariate analysis identified that higher proportions of antiresorptive drugs prescriptions were associated with female patients (OR 11.40, 95% CI: 1.5–84.3, $P = 0.02$), an age of 40 years or more (OR 3.22, 95% CI: 1.3–8.3, $P = 0.02$) and to consume a

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lower number of cointerventions with other drugs (OR 1.09, 95% CI: 1.0–1.2, $P = 0.03$). Corticosteroid treatment was not associated with the prescription of antiresorptives ($P = 0.31$). In conclusion, a low proportion of Mexicans with RA receive antiresorptive therapy independently regardless of whether they consume or not chronically corticosteroids. Additional strategies should be evaluated to encourage the prevention and early treatment for osteoporosis in patients with RA.

Keywords Osteoporosis · Glucocorticoids · Antiresorptives · Rheumatoid arthritis

Introduction

In Mexico, around 30% of patients with rheumatoid arthritis (RA) receive chronic glucocorticoids treatment [1]. These drugs are commonly used as an adjuvant therapy in order to control symptoms including pain, inflammation and functional impairments [2, 3]. It is widely known that in RA, both disease activity and glucocorticoids therapy have been associated with osteoporosis and bone fractures [4–8]. We previously reported that 25% of Mexican women with RA had osteoporosis [9]. Being this osteoporosis a major risk factor for fractures that may lead to disability, depression and a decreasing in life expectancy, it is necessary to implement strategies based on clinical practice guidelines for the prevention of osteoporosis in RA [10].

In 2001, the American College of Rheumatology (ACR) Ad Hoc Committee on glucocorticoid-induced osteoporosis recommended that patients receiving glucocorticoid therapy, particularly prednisone or its equivalent, at a dose ≥ 5 mg/day with a duration for ≥ 3 months should also receive preventive therapy for osteoporosis based on bisphosphonates and calcium/vitamin D supplements [10]. To this regard, a number of clinical trials have shown the efficacy of bisphosphonates therapy for preventing and treating glucocorticoid-induced osteoporosis [11–16]. The FDA and the National Osteoporosis Foundation (NOF) recommend alendronate and risedronate for the prevention of and treatment for osteoporosis in patients who are either initiating or taking corticosteroids [17].

Although, to date, these recommendations for preventing and treating glucocorticoid-induced osteoporosis are widely supported, in RA there is a considerable variation in the prescription of antiresorptive therapies. Solomon et al. have observed that in RA, only about a 40% of patients taking glucocorticoids ≥ 5 mg for ≥ 3 months received osteoporosis management [18], whereas other authors have reported lower rates of antiresorptive prescriptions in these patients [19, 20].

In Latin America, no studies have described the frequency of prescribing antiresorptive therapies for patients with RA taking chronic glucocorticoid therapy. Therefore, we conducted a cross-sectional study with the aim to identify the prescription rate for bisphosphonates and other antiresorptive drugs used to prevent and treat glucocorticoid-induced osteoporosis in Mexican patients with RA.

Materials and methods

Design

Cross-sectional study.

Clinical setting

The study included 520 patients with a diagnosis of RA who were evaluated from January to March 2010 in an outpatient rheumatology clinic of a secondary-care center in Guadalajara, Mexico (Hospital General Regional 110, IMSS). Inclusion criteria were a definite diagnosis of RA according to the examining rheumatologist and 1987 American College of Rheumatology (ACR) criteria, entries on a daily consultation sheet and an available clinical chart available. Exclusion criteria were an indefinite diagnosis of RA, an overlapping syndrome, inclusion in other research protocols or a previous inclusion in a clinical trial for osteoporosis management. The hospital characteristics were described elsewhere [21]: briefly, all the patients were examined by one of the three rheumatologists attending in that clinic or, alternatively, by one of three internal medicine specialists in the absence of the rheumatologists. Each rheumatologist or internal medicine specialist regularly performed an average of 20 to 25 consults/day, where at least 47% were for patients with RA. At our center in 2010, the antiresorptive drugs authorized for prescription in rheumatology for preventing or treating osteoporosis included alendronate, risedronate and zoledronic acid. All of these drugs were provided by the social medical insurance without additional cost to the patients' pocket. In this secondary-care hospital is no equipment available for the measurement of bone mineral density. The bone densitometer service is restricted according to clinical and administrative criteria. Therefore, requests to perform a bone mineral densitometry for RA or other chronic diseases had to be justified, approved and authorized by both a head of the department and administrative manager. However, the number of authorizations for densitometry is limited by the budget and number of solicitudes of other departments. Therefore, patients included in this study had no measurement of bone mineral density.

Data collection

After the medical visit, a chart was filled out daily by one physician. Two trained fellow researchers created an electronic database with all the information from the clinical note recorded at the time of consultation. The information included name, code, diagnosis, age, gender, type of job, number of visit, comorbidities, drugs prescribed and the total number of drugs prescribed as cointerventions. Treatments for RA included disease-modifying antirheumatic drugs, nonsteroids, anti-inflammatory and biological agents, glucocorticoid therapy and corticosteroid dosage. The assessment of type and dosages of any antiresorptive agents received and whether patients received calcium and vitamin D supplements as well as other cointerventions was crosschecked in both clinical chart and administrative database of the hospital.

Statistical analyses

Qualitative variables were expressed as frequencies and percentages (%); quantitative variables were expressed as medians and ranges. Prevalence and its 95% confidence intervals (95% CI) of prescriptions for antiresorptives were computed. In the univariate analysis, we used χ^2 test for comparisons of proportions between two subgroups: patients who received (a) and did not receive (b) antiresorptive therapy. A logistic regression analysis was performed to evaluate variables associated with the prescription for antiresorptive therapy (dependent variable). The covariates used in the model in order to adjust

those factors influencing the prescription of antiresorptives included age, gender, presence of comorbidity and total number of medications prescribed other than antiresorptive agents. The odds ratios (ORs) and their 95% CI were computed. Statistical significance was set at ≤ 0.05 . All analyses were performed with SPSS version 8.0.

Results

Of 1,264 patients who were attended in rheumatology consult during the study period, 744 patients were excluded for the following reasons: 539 had a diagnosis other than RA and 205 patients had an undefined diagnosis (Fig. 1). Therefore, a total of 520 adults with RA were included in the study.

Table 1 shows the clinical characteristics of these subjects. Most patients were women (88%), and 80% were 40 years old or more. Nearly half (45%) had one or more comorbidities including hypertension ($n = 64$; 12%), diabetes mellitus ($n = 36$; 7%) and hypothyroidism ($n = 14$; 3%). For treating RA, 93% received one or more disease-modifying antirheumatic drugs, and only 8% received anti-TNF α agents; in contrast, prednisone or its equivalent was prescribed for 79% of patients, and 21% received doses of ≥ 7.5 mg/day. Calcium and vitamin D supplements were prescribed for 20% (95% CI: 16.8–23.9), but antiresorptive agents were prescribed for only 13% (95% CI: 10.0–15.9) of patients. The antiresorptive drug prescribed most often was alendronate (8.5%, 95% CI: 6.2–11.2), followed by raloxifene (4.2%, 95% CI: 2.7–6.3). Of the 409 (79%)

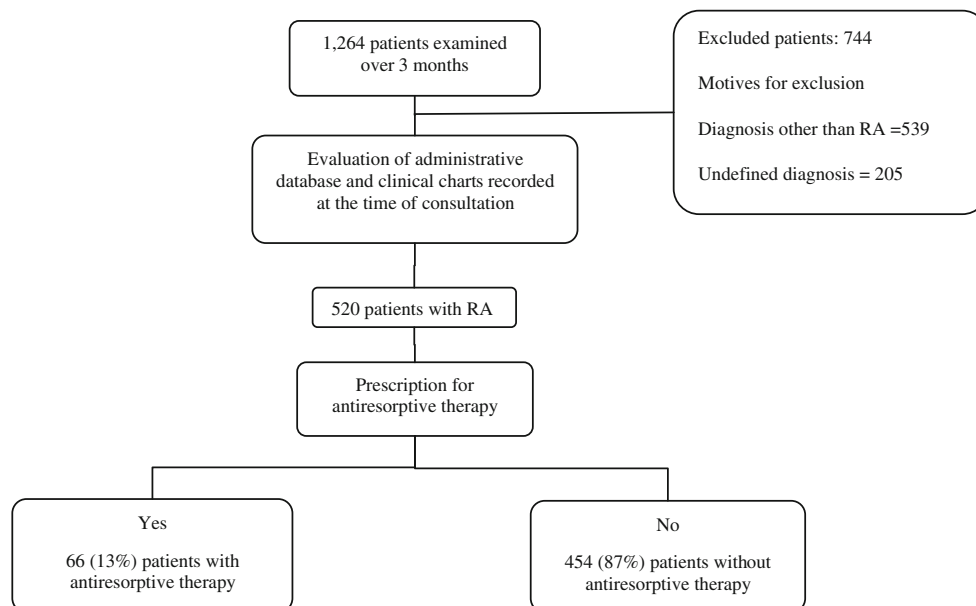


Fig. 1 Study flowchart

Table 1 Patient characteristics and treatments for rheumatoid arthritis

General characteristics	Frequency (%) <i>n</i> = 520
Female gender	456 (88)
Age ≥40 years	414 (80)
Age (mean ± SD)	52 ± 14
Salaried worker	178 (34)
Subsequent visit*	356 (89)
Comorbidities	232 (45)
DMARDs	482 (93)
Methotrexate	346 (67)
Sulfasalazine	222 (43)
Azathioprine	140 (27)
Chloroquine	152 (29)
D-Penicillamine	48 (9)
Anti-TNF agents	43 (8)
NSAIDs	461 (89)
Corticosteroids (prednisone or equivalent)	409 (79)
Prednisone	293 (56)
Corticosteroid dose ≥7.5 mg/day	111 (21)
Calcium and vitamin D supplementation	105 (20)
Antiresorptive therapy	66 (13)
Alendronate	44 (9)
Zoledronic acid	1 (0.2)
Raloxifene	22 (4)

* Information about the variable “subsequent visits” was available in 400 patients. Prednisone and deflazacort doses mean (mg/day) 4.66 ± 3.4 and 6.43 ± 2.3, respectively; DMARDs: D-penicillamine 48 (9%); anti-TNFα agents: etanercept 34 (7%), infliximab 8 (2%). No patients in this study received risdroneate. Qualitative variables are expressed as frequency and percentages (%), and quantitative variables are expressed as means ± standard deviation (SD).

DMARDs disease-modifying antirheumatic drugs, TNF tumor necrosis factor, NSAIDs non-steroid anti-inflammatory drugs

patients who received corticosteroid therapy, only 59 received antiresorptives (14%, 95% CI: 10.9–18.6).

Table 2 shows the comparisons between patients who did versus did not receive antiresorptive therapy. The results showed that the prescription of antiresorptives was associated with female gender ($P = 0.005$), age 40 years or more ($P = 0.006$), systemic arterial hypertension ($P = 0.02$) and a prescription for calcium and vitamin D supplements ($P < 0.001$).

Table 3 shows the multivariate analysis performed to identify variables associated with the prescription of antiresorptive therapy. In the logistic regression model, the following variables were identified: female gender (OR 11.40, 95% CI: 1.54–84.37, $P = 0.02$), age 40 years or more (OR 3.22, 95% CI: 1.25–8.34, $P = 0.02$) and a low number of other prescribed medications different to antiresorptives (OR 1.09, 95% CI: 1.01–1.17, $P = 0.03$). Taking

Table 2 Comparison of characteristics between patients who received antiresorptive therapy and patients without antiresorptive therapy

Variable	With antiresorptive therapy <i>n</i> = 66 (13%)	Without antiresorptive therapy <i>n</i> = 454 (87%)	<i>P</i>
Female gender	65 (99)	393 (87)	0.005
Age, mean ± SD	60 ± 13	51 ± 13	<0.001
Age ≥40 years	61 (92)	353 (78)	0.006
Salaried worker	16 (24)	162 (36)	0.07
Subsequent consult ^a	49/50 (98)	307/350 (88)	0.03
Comorbidity			
Arterial hypertension	14 (21)	50 (11)	0.02
Diabetes mellitus	4 (6)	36 (7)	0.8
Hypothyroidism	4 (6)	11 (2)	0.1
DMARDs			
Methotrexate	42 (64)	304 (67)	0.6
Sulfasalazine	30 (46)	142 (42)	0.7
Azathioprine	23 (35)	117 (26)	0.1
Chloroquine	16 (24)	136 (30)	0.3
Anti-TNF	8 (12)	35 (8)	0.2
Prednisone doses (mg/day), mean ± SD	5.5 ± 3.1	4.5 ± 3.4	0.025
Prednisone or equivalent doses ≥7.5 mg	19 (29)	92 (20)	0.1
Calcium, vitamin D	54 (82)	51 (11)	<0.001

^a Subsequent consults was not always completed in the daily records. Denominator represents the total number of patients for whom the variable was recorded.

P values were obtained for qualitative variables with a chi-square or Fisher exact test, when required; for quantitative variables, *P* values were obtained with the unpaired Student's *t*-test.

DMARDs disease-modifying antirheumatic drugs, TNF tumor necrosis factor

Table 3 Multivariate analysis results for factors associated with the prescription of antiresorptive therapy

Variable	OR	95% CI	<i>P</i>
Female gender	11.40	1.5–84.3	0.02
Age ≥40 years	3.22	1.3–8.3	0.02
Comorbidity ≥1 chronic disease	0.82	0.3–1.9	0.66
Prednisone or equivalent ≥7.5 mg/day	1.48	0.8–2.7	0.31
Low number of drugs received (excluding antiresorptives)	1.09	1.0–1.2	0.03

Analysis performed by logistic regression using the ENTER method. OR odds ratio, 95% CI 95% confidence intervals, *P* statistical significance set at ≤ 0.05.

glucocorticoids was not associated with the prescription of antiresorptive therapy (OR 1.48, 95% CI: 0.8–2.7, $P = 0.31$).

Discussion

This study showed a low prevalence of prescriptions for bisphosphonates and other antiresorptives drugs for Mexican patients with RA either initiating or taking chronically glucocorticoids. Prescription of antiresorptive therapy was associated with to be women, over 40 years old and had a relatively low number of prescriptions for other drugs. Although a high rate of corticosteroid prescriptions (79%) was observed, corticosteroid utilization was not a determinant factor for the prescription of antiresorptives in this population.

To date, there is no other study performed in Mexican patients with RA evaluating the prevalence of prescription of antiresorptive treatments. Several studies on other countries have observed a similar prevalence of antiresorptive prescriptions compared with the obtained in our study. Peat et al. [22] identified that only 6% from 214 patients treated with corticosteroids received antiresorptives, whereas Walsh and coworkers analyzing 303 patients treated with corticosteroids (69 with RA) identified that only 14% had antiresorptive therapy [20]. More recently, Feldstein et al. [23] found that only 15% of 3,031 patients treated with corticoids (17% with RA) received antiresorptives, whereas higher prevalence rates for antiresorptive prescription in RA were identified by Solomon et al. [18, 19], varying from 35 to 42% in two separate studies. Based on the guidelines for the prevention of and treatment for glucocorticoid-induced osteoporosis from the American College of Rheumatology, these prescription rates are critically low [10]. Although many factors may influence the prescription rate of bisphosphonates for patients with RA, most of the studies confirm a suboptimal prescription rate in different countries and settings [18–20, 22, 23].

In Mexican women with RA, the prevalence of osteoporosis is around 25% [9]. Although osteoporosis per se increases the risk of fractures, corticosteroid utilization may potentiate this risk, being the incidence of new fractures as high as 17% after 1 year of receiving corticosteroids [24]. According to the guidelines proposed by the ACR Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis, patients with prednisone at doses of 5 mg/day over a period of 3 months or more should receive simultaneously bisphosphonate therapy and calcium/vitamin D supplements in order to decrease the risk of fracture [10]. Thus, the results of the present study suggest that the lack of an appropriate prescription of bisphosphonates would be a factor to increase the incidence of fractures, increasing morbidity, cost and healthcare requirements in these patients.

A relevant issue that was not addressed in our study is whether the limitations in obtaining a bone mineral densitometry for our patients with RA may influence the

clinicians' decision of not to prescribe antiresorptive; this is because clinicians may consider that they would require the results of this diagnostic test previously to indicate bisphosphonates. If this is the case, it would be logical to consider that the prescription of antiresorptive drugs would increase significantly following to a wider access to perform bone densitometry. Unfortunately, many (if not the most) hospitals of the Public Health Insurance network in Mexico may experience similar difficulties that the present hospital experience in performing bone mineral densitometry for most patients with RA due to lack of equipment, cost and long waiting list. Nevertheless, we propose that the behavior to prescribe antiresorptives should not be determined exclusively by the availability of testing bone mineral density. Different studies have shown bisphosphonate efficacy in glucocorticoid-induced osteoporosis [12–14]. Therefore, we suggested that prescription for bisphosphonates should be increased for patients with RA, particularly for those treated with corticosteroids for 3 months or more independently of the bone mineral density results. Some other limitations are also observed in our study. First, we evaluated only the clinical notes at the index visit; therefore, we could not exclude the possibility that some patients had received antiresorptive drugs in the past and treatment could be withdrawn for different reasons. Future studies should consider a more rigorous cohort design that can identify the incidence of past antiresorptive prescription and factors associated with discontinuation. Another limitation was the lack of complete information about other factors that may have influenced their prescription, including illness duration, fractures history or prostheses.

In summary, this study showed a very low prevalence of prescriptions for antiresorptive therapy; furthermore, prescribing this therapy was not influenced by ongoing corticosteroid therapy despite the doses. This work was the first to investigate the prevalence of antiresorptive therapy in Mexican patients with RA who were at high risk of developing osteoporosis due to chronic glucocorticoid therapy. This area of research could positively influence the prevention of and treatment for glucocorticoid-induced osteoporosis by making rheumatologists aware of the lack of preventive measures compared with the international recommendations for avoiding the development of osteoporosis and its complications.

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