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Use of osteoporosis drugs in patients with recent-onset rheumatoid arthritis in Finland

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ABSTRACT

Objective. *We investigated the implementation of pharmaceutical osteoporosis (OP) prevention in early rheumatoid arthritis (RA) in Finland.*

Methods. *All incident RA cases from 2000 to 2007 were identified using the national register of the Social Insurance Institution (SII) as the sole source. The use of calcium and vitamin D preparations and OP drugs during the first year was evaluated.*

Results. *A total of 14,878 incident RA patients were found. They had a mean age of 56 (SD 15) and 68% were female. Nine per cent of the total number, which equated to 11% for women and to 5% men, had purchased OP drugs. The use of OP drugs increased over time: in the 2006–2007 period, relative risk (RR) for purchase was 1.62 (95% CI 1.38–1.92) for women and 2.1 (1.34–3.30) for men compared to the 2000–2001 period.*
Over the 2000–2005 period, 49% of females and 52% of males used glucocorticoids (GCs) during the first year. Among the GC-users, 38% of women and 24% of men also received calcium and vitamin D preparations by prescription, and 14% of women and 6% of men also used OP drugs. For GC users, the female sex, and older age increased the risk for OP use: the respective RRs were 1.45 (95% CI 1.31–1.61), 2.54 (95% CI 2.21–2.91), and 1.060 (95% CI 1.057–1.065).

Conclusion. *Patients with early RA are increasingly receiving OP drugs, and the use is more frequent among patients with known risk factors.*

Introduction

Rheumatoid arthritis (RA) is one of the well-known risk factors of osteoporosis (OP) (1-4). Inflammation causes bone resorption, which may occur early during the disease course. Periarticular osteopenia is actually one of the American College of Rheumatology 1987 classification criterion for RA (5). Systemic OP in RA is more pronounced in the hip and the radius than in the axial skeleton and is also associated with the severity of RA (6, 7). Glucocorticoids (GCs) are commonly added on to disease-modifying anti-rheumatic drugs (DMARDs) to control inflammation in the treatment of RA (8, 9). Nonetheless, the GCs may aggravate OP, especially in the lumbar spine, though the benefit-risk ratio for this event varies between individual RA patients and also according to the dosage of GCs (5, 10). The fracture risk for patients taking GCs is, however, not exclusively associated with bone mineral density (BMD) (11, 12).

The general risk factors for OP and fractures are present in RA patients, as well (3). Older age increases the prevalence of OP, and half of incident patients with RA are 58 years of age or older in Finland (13). About two-thirds of the patients are women, who at menopause are prone to a major loss of bone mass. Physical activity protects against OP (14). RA patients are less physically active compared to the general population. One of the reasons is the loss of functional capacity (15). Disability as such is a risk factor for OP and also increases risk of falling, which is a major contributor to fractures (16). Active drug treatment limits disease-associated bone loss by several mechanisms (17). Suppression of inflammation restores normal bone turnover, and recovering functional capacity enables physical exercise.

Calcium intake is related, albeit weakly, to BMD (18). Calcium supplementation either alone of in combination with vitamin D reduces the risk of fracture (19). Vitamin D deficiency is prevalent in the general population and among RA patients (20).

Both the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) have published recommendations for the prevention of OP in patients with rheumatic diseases and who receive GC treatment (21, 22). When an RA patient is started on prednisolone ≥7.5mg daily for over three months, calcium and vitamin D supplementation should also be prescribed. Antiresorptive therapy should be considered when fracture risk factors are present.

We evaluated the implementation of these guidelines among Finnish patients with recent-onset RA.

Materials and methods

Finland provides a general health in-

surance that covers the entire population. The Social Insurance Institution (SII) reimburses 42% of the costs of medication prescribed by a doctor. Patients with certain chronic and severe diseases such as RA are entitled to a special, higher reimbursement rate (72 or 100%) to defray drug costs. To establish entitlement, a patient must file a doctor's certificate based on clinical examination by a rheumatologist that: describes the appropriate diagnostic procedure, gives the ICD-10 code, and provides a treatment plan according to good clinical practice.

Reimbursement decisions are recorded in a nation-wide register. From this register we obtained incident cases of RA, *i.e.* those patients who during the period from 1.1.2000 to 31.12.2007 were granted special reimbursement for medications for RA (DMARDs and GCs) for the first time. The ICD-10 codes M05 and M06 were used to identify the patients. The register data included sex, date of birth, and date of the reimbursement decision, defined as the index day.

The SII also keeps a prescription register that collects and stores data on all purchases of all reimbursed drugs including the date of purchase, the amount of medication and the Anatomical Therapeutic Chemical classification (ATC) code of the drug.

By means of these registers we obtained data on the OP medication that incident patients with RA had purchased. We focused exclusively on medication during the first treatment year. We included information for 30 days before and up to 365 days after the index day to take into account the medications bought after the first doctor visit but before the reimbursement decision. We analysed data of four two-year periods: 2000-1, 2002-3, 2004-5, and 2006-7.

In Finland, preparations that contain calcium and vitamin D, which are also used in OP preventions, are available over the counter so we could not obtain data on their overall use. Many preparations, however, are included in the reimbursement system and reimbursed (42%) to the patient, if purchased to fill a doctor's prescription. We gathered data on these purchases.

Some GC preparations were temporarily excluded from the reimbursement system during the years of 2006 and 2007, which caused some bias. Consequently, we analysed GC use only from 2000 to 2005 inclusive.

Hormone replacement therapy (HRT) was not included, because it is indicated mainly for other reasons than OP *per se*. The prescription register does not collect data on medications used in hospitals and institutions.

Statistics

Results were expressed as means with standard deviation (SD) and the 95 per cent confidence intervals (95% CI) were calculated for the most important outcomes. A generalised linear model with the binomial family, log link, was used to produce the adjusted relative risk (RR).

Results

We identified 14,878 incident cases of RA from 01.01.2000 to 31.12.2007. Of these, 10,119 (68%) were female and 4,739 (32%) were male. Their mean ages were 57 (SD 14) and 56 (SD 15) years, respectively. Fifty-five per cent of female patients were 55 years of age or older and thus most probably postmenopausal.

A total of 1,351 (9%) patients with RA (11% of females and 5% of males) had purchased OP drugs during the first year after commencement of antirheumatic treatment. Women were more prone to using OP medication. Consequently, the age-adjusted relative risk (RR) of purchase was 2.60 (95% CI 2.26 to 2.99) for women compared to men.

Bisphosphonates constituted the bulk of purchases (Table I). Calcitonin was used by 7%. Purchases of selective oestrogen receptor modulators (SERMs) and parathyroidhormone analogues (PTHan) were almost negligible.

During the first year, 26% of the patients (29% of females and 19% of males) received calcium and vitamin supplementation by doctor's prescription.

The use of OP drugs during the years 2006 to 2007 increased over time compared to 2000–2001. RR (95% CI) for purchase was 1.62 (1.38–1.92) in women and 2.1 (1.34–3.30) in men.

Table I. Proportions of initial OP drugs used during the first treatment year by 1351 patients with early RA in Finland from 2000 through 2007.

First OP drug	Patients n. (%)
Alendronate	803 (59)
Risedronate	360 (27)
Etidronate	51 (4)
Ibandronate	37 (3)
Clodronate	4 (<1)
Calcitonin	98 (7)
Parathyroidhormone analogue	1 (<1)
Raloxifene	9 (<1)

During the years 2006–2007, 12% of women and 5% of men bought OP medication within 365 days of the index day. The highest proportion was found for the age group 75 to 79 years. Figure 1 shows the use by age-group in 2000–2003 and 2004–2007.

The early use of methotrexate medication may be used as a proxy of active RA. Methothexate was used by 58% of women and by 56% of men during the first year. Patients on OP medication received methotrexate marginally more often (in women 61% and in men 57%,) than other DMARDs.

During the period 2000 to 2005 inclusive, about half of the RA patients (49% of females and 52% of males) used GCs in their first drug treatment year. There were no data on the GC dosages, but the common practice in Finland is to prescribe a small dose, usually from 5 to 7.5 mg of prednisolone daily. Of the RA patients that took GCs, 38% of women and 24% of men received concomitant calcium and vitamin D preparations by prescription during the same year, whereas the respective percentages for patients without GCs were 21% and 13%. Of the GS users, 14% of women and 6% of men were prescribed OP drugs. In contrast 8% of females and 3% of males not taking GCs received OP medication.

In the multiple regression analysis, the GC use was determined as a "risk factor" for OP medication: its risk ratio (RR) was 1.45 (95% CI 1.31–1.61), whereas being female had RR of 2.54 (95% CI 2.21–2.91) and higher age had RR of 1.060 (95% CI 1.057–1.065).

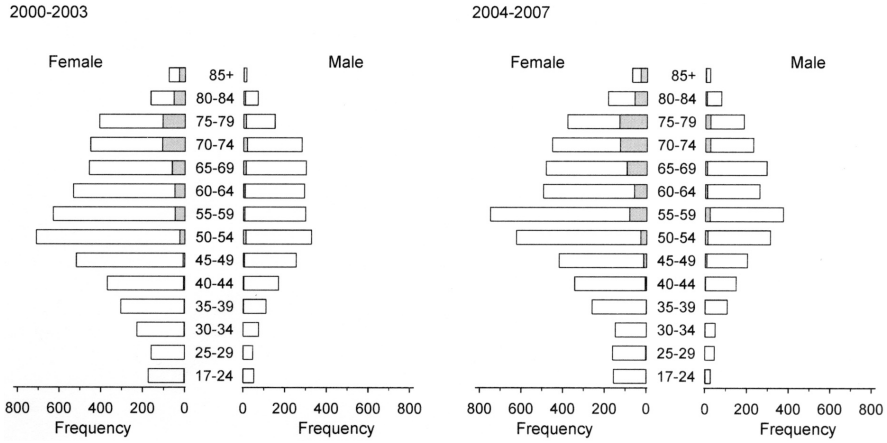

Fig. 1. Use of OP drugs during the first treatment year among incident patients with RA by age and the year when contracted RA. The columns represent the cumulative number of patients and the shaded part the number of patients, who purchased OP drugs.

Discussion

The prevention of osteoporosis and fractures in patients with RA is a recognized issue among rheumatologists, but there is only scant information on the implementation of the published recommendations. To the best of our knowledge, this is the first report that focuses on the use of fracture-preventing drugs in recent-onset RA.

Our study has the advantage of availability of nationwide official register data. Our case definition was based on eligibility for special reimbursement for DMARDs used in the treatment of RA, *i.e.* a clinical diagnosis of RA by a rheumatologist and the need to initiate antirheumatic medication. No data were available on the fulfilment of the ACR classification criteria for RA, but the use of antirheumatic medication can be regarded as highly indicative for an actual diagnosis of RA. The mean annual incidence of RA from 2000 through 2007 was 44.5 per 100,000 (13), which is congruent with epidemiological data from Nordic countries and the US. Our data comprise the medications that the patients actually bought and, consequently, are more reliable than those based on self-report or patient records. Because calcium and vitamin D preparations are available over the counter, the percentages (42% reimbursement by prescription), we report in this study are an underestimate. It is probable, however, that for economic reasons, most of the long-term and regular supplementation of calcium and vitamin D is included in the prescription register. We have no data about the self-initiated use of these preparations.

In Finland, about half of new RA patients receive GCs as a part of their first-year treatment strategy, and the GCs are almost invariably prescribed in combination with one or more DMARDs. From 2000–1 to 2004–5, the proportion of RA patients who used GCs as a part of their initial drug treatment increased by 22% (9). The current guidelines recommend low-dose GCs, *i.e.* 5–10mg of prednisolone, but we have no data about the actual dosage.

Over the study period, anti-rheumatic treatment became increasingly intensive in Finland as 69% of patients received methotrexate and 55% received a combination of at least two DMARDs during the first treatment year in 2006-7 compared with 2000–1 (9). Obviously, early suppression of rheumatic inflammation has a favourable impact of bone health with less need for OP prevention.

Previous knowledge regarding the implementation of osteoporosis prevention among RA patients relies mainly on patient chart reviews in those individuals with established RA, and such reports are not comparable with our results. In one health maintenance organisation based study the focus was in early prevention of OP, but at the cohort of 3031 only 17% were RA patients, and mean GC dose was markedly high at the equivalent of 20mg prednisolone (23). Moreover, only 15% of the cohort (18% of women, 9% of men) received anti-resorptive therapy other than HRT.

In a UK study, the general practice records one third of 62,230 women aged 50 and older were sampled (24). Of the sample, 3.2% were prescribed GCs. Mean duration of GC treatment at the time of study was more than 3 years and the cumulative dose was 1.5g per year. About 47% of GC users received either HRT, bisphospohonates, or calcium supplements. The use of HRT was greatest for the age group 50-59 (41%) and became less frequent with older age. At the same time, the percentage of women who received bisphosphonates grew from 8 (50–59 years) to 26 (70–79 years).

Summarising the data from clinical cohorts of established RA with mean durations of several years, the adherence among physicians to OP prevention and treatment guidelines has been poor, nevertheless, some improvement can be seen (25-28). A recent follow-up study suggests, that despite OP drugs, fracture prevention is still a problem (29).

Which incident RA patients who would benefit from medication for fracture prevention actually got the proper prescriptions, is a crucial question. Our results give no accurate answer, because we have no data on disease activity, functional capacity, dose and duration of GC treatment, the general risk factors of OP, and any BMD measurements made. A good proportion of our patients were prescribed calcium and vitamin D supplementation. The use of antiresorptive drugs was more frequent among RA patients with risk factors, *i.e.* in women, older patients, and those using GCs.

In conclusion, our results suggest that OP prevention among patients with recent-onset RA has become more effective. Further studies on patient cohorts with more detailed data on relevant risk factors are needed to establish, whether the current practices in prevention are sufficient.

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