

Proper time to initiate antiosteoporotic treatment in rheumatoid arthritis with or without glucocorticoid use

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See Article on Page 509-515

Rheumatoid arthritis (RA) is a systemic autoimmune disease, characterized by inflammation in multiple joints, particularly the small joints of the hands and feet. Joint inflammation is induced primarily by autoreactive immune cells (T- and B-cells and macrophages) and the overproduction of proinflammatory cytokines, especially tumor necrosis factor- α , interleukin (IL)-1 β , IL-6, and IL-17, which are centrally involved in the pathogenesis of RA. These autoreactive immune cells and proinflammatory cytokines mediate long-term cartilage degradation and bone erosion, resulting in joint dysfunction. Furthermore, these immunological factors may increase the risk of osteoporosis and fracture in RA patients by enhancing osteoclastogenesis [1].

In addition to autoreactive immune cells, proinflammatory cytokines, and receptor activator of nuclear factor- κ B ligand, patients with RA may be exposed to disease-specific risk factors of osteoporosis and fractures, including disability in daily activities, immobilization, and decreased function in digestion and absorption. Drugs used for the treatment of RA can also affect the reduction in bone mineral density

(BMD). Cyclosporine, tacrolimus, methotrexate, and glucocorticoids have been reported to be directly associated with osteoporosis [2].

With the need to prevent osteoporotic fractures in RA, Kanis et al. [3] developed a new fracture risk assessment tool (FRAX), based on the use of clinical risk factors alone and/or in combination with BMD, that assessed the 10-year probability of hip fracture as well as a major osteoporotic fracture. The clinical factors in FRAX include both glucocorticoid use and RA, in addition to 'traditional' risk factors, such as gender, body mass index, a prior history of fracture, a parental history of hip fracture, secondary osteoporosis, and frequent alcohol intake [3].

According to a previous report, recruiting 234 postmenopausal women and men over 50 years of age with seropositive RA, 52% patients had osteoporosis by the World Health Organization criteria and, by FRAX, the 10-year fracture risk was 13% for major osteoporotic fractures and 3.5% for hip fractures. Moreover, 56% patients by the criteria of the Korean Health Insurance Review Agency, 54% patients by FRAX and 65% patients according to the National Osteoporosis Foundation (NOF) guidelines, needed treatment for osteoporosis. In this study, RA itself was

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determined to be a high risk factor for fracture, and thus the authors suggested that the automatically calculated FRAX should be considered first, before an assessment of BMD [4].

Glucocorticoids are often used in patients with RA to alleviate symptoms or quench acute inflammation. However, despite their anti-inflammatory effects, glucocorticoid use is a strong risk factor for the development of osteoporosis, as mentioned above. Glucocorticoids enhance bone resorption by decreasing serum estrogen and testosterone levels, reducing calcium absorption, and increasing renal excretion of calcium, leading to a decrease in serum calcium levels and an increase in serum parathyroid hormone levels. In contrast, glucocorticoids decrease bone formation by direct actions on bone cells, reducing serum testosterone levels and muscular strength. Therefore, glucocorticoid use is related to early rapid bone loss in patients with RA who are taking or begin to take glucocorticoids; the decline in BMD begins with 3 months of glucocorticoid use and peaks at 6 months [5,6].

With these concerns, the American College of Rheumatology (ACR) 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis (GIOP) were promulgated and are used currently. These recommendations incorporated the FRAX risk assessment tool and femoral neck BMD and classified postmenopausal females, and males over 50 years of age with a history of glucocorticoid use into high (> 20%), medium (10% to 20%), and low (< 10%) risk of fracture, according to the 10-year probability of a major osteoporotic fracture. These recommendations suggested the initiation of antiosteoporotic treatment in patients with anticipated glucocorticoid use or those on current glucocorticoid therapy for over 3 months, except those with a dose < 7.5 mg/day in the low-risk group [6,7]. The ACR 2010 recommendations first proposed new guidelines for the prevention of GIOP in patients with RA, but they left a question as to whether they should be applied to patients with RA who did not take glucocorticoids. That is, the ACR 2010 recommendations for the prevention of GIOP are not applied evenly to all patients with RA. Furthermore, although the NOF guideline incorporated the 10-year probability of a fracture by FRAX, including glucocorticoid use and RA, the NOF guidelines may not be sufficient to propose specific guidelines for GIOP in

RA [6-8].

With this background, Lee et al. [7] recently compared the ACR 2010 recommendations for GIOP and the NOF guideline to evaluate whether the ACR 2010 recommendations for GIOP were sufficient for identifying candidates for antiosteoporotic treatment in patients with RA, regardless of glucocorticoid use. They enrolled 100 postmenopausal females over 50 years of age with RA. When they applied the ACR 2010 recommendations for GIOP and NOF guideline simultaneously to only the 57 patients who were currently taking glucocorticoids, they found a high agreement rate between the two guidelines ($\kappa = 0.76$). They also applied the two guidelines to all patients (the 57 with glucocorticoid use + the 43 without). When they used only the ACR 2010 recommendations for GIOP, 39% patients were identified as candidates for antiosteoporotic treatment. However, when they applied the NOF guidelines, the number of candidates for antiosteoporotic treatment increased to 56% (two and 19 patients belonging to the low-risk and not eligible for GIOP recommendation groups, respectively). Moreover, when they added screening radiography for vertebral fractures to the two guidelines, 67 patients needed antiosteoporotic treatment [7].

The goal of antiosteoporotic treatment is to prevent not only the development of osteoporosis, but all kinds of fractures. According to the Rotterdam Study, which enrolled 2,437 men and 3,357 women over 55 years of age, hip fracture was observed in 58% of males and 31% of females whose BMD ranged from -1.0 to -2.5 [9]. Furthermore, the risk of all fractures in the osteopenia group was higher than in the normal group, with a fracture rate ratio of 1.80 [10]. Thus, the initiation of antiosteoporotic treatment should not be confined to subjects with BMD T score less than -2.5 , but it should also be considered in subjects with a BMD T score less than -1 , when, by FRAX, they have a 10-year probability of hip fracture above 3% or a 10-year probability of a major osteoporotic fracture above 20%.

Not all patients with RA are taking glucocorticoids and it may be difficult to identify a history of glucocorticoid use in clinical situations. Also, it is not possible to assess the total duration of glucocorticoid use or the cumulative dose even in patients who have received glucocorticoids. Also, considering that fractures can occur in subjects with osteopenia-range BMD, physicians should

be encouraged to apply one more the guidelines for antiosteoporotic treatment other than the ACR 2010 recommendations for GIOP to patients with RA regardless of glucocorticoid use, to reduce the fracture rate by early detection and treatment.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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