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This thesis focuses on the effect of inflammatory activity and anti-inflammatory treatment on bone mineral density (BMD) loss in recent-onset rheumatoid arthritis (RA), and on localized BMD loss and the effect of tumor necrosis factor alpha (TNF α) inhibition in (secondary) hand osteoarthritis (OA).

Chapter 1 gives a general introduction on RA and OA, addressing especially etiology, bone destruction, including joint damage and BMD loss, and treatment options.

With regard to RA, in the past decade a revolution took place in the treatment of patients diagnosed with the disease. New developments in anti-rheumatic treatment, including the advent of biologicals, the more early and intensive treatment approach, and validated monitoring tools resulted in better disease outcomes, higher quality of life, and decrease in sick leave; in other words less burden on patient and society.

The BeSt study, acronym for Behandel Strategieën, i.e. treatment strategies, pulls its weight on this revolution. The inventors of the BeSt study introduced a novel study design comparing four different treatment strategies in which treatment adjustments were made continuously when low disease activity, defined as disease activity score (DAS) ≤ 2.4 , was not reached in patients with recent-onset RA. On the other hand, treatment could be tapered to monotherapy in a maintenance dose, and thereafter even to zero when longstanding, i.e. six consecutive months, low disease activity, DAS ≤ 2.4 , or clinical remission, DAS < 1.6 , was reserved. The treatment strategies were: group 1. sequential monotherapy starting with methotrexate (MTX), group 2. step-up combination therapy starting also with MTX, group 3. initial combination therapy with MTX, sulphasalazine and quickly tapered high dose of prednisone, and group 4. initial combination therapy with MTX and TNF α inhibitor infliximab. In the initial combination groups, group 3 and 4, low disease activity was reached earlier, and therefore a greater reduction of joint damage progression was seen compared to the initial monotherapy groups, group 1 and 2.[1] The studies described in **chapters 2-6 and 8** have been conducted as part of the still ongoing BeSt study.

One of the hallmarks of RA is bone destruction, including joint damage, and localized and generalized BMD loss. It is known that the inflammation-driven, activated osteoclast, mediated particularly through the osteoprotegerin/receptor activator of NK-kappaB ligand (OPG/RANKL) signaling system, is the most crucial cell in the pathogenesis of joint damage. The direct effect of this inflammation-driven mechanism on BMD loss is less clear. When inflammatory activity plays an important role in the etiology of BMD loss, anti-inflammatory treatment might influence this towards less BMD loss. Nevertheless, on the other hand, the in RA frequently used corticosteroids are notorious in having a catabolic effect on bone. Localized BMD loss in the hands is proposed as an outcome measure for bone involvement in RA. The value of localized BMD loss in an early stage of the disease to predict subsequent destructive disease, compared to other well-known predictors, is not clear. It is thought that, just as in RA, inflammatory activity might play an important role in the development and progression of hand OA. Consequently, strong anti-inflammatory agents, such as TNF α inhibitors, might diminish or stop bone destruction in hand OA.

In this thesis, the relation between inflammation, and localized and generalized BMD loss was investigated in recent-onset RA. The effect of novel, dynamic treatment strategies with anti-rheumatic drugs, including corticosteroids and anti-TNF α , and anti-resorptive drugs on BMD loss was studied. Furthermore, the value of localized BMD loss in the hands to predict subsequent joint destruction, in comparison to other well-known predictors, was analyzed. The role of inflammation in progression of hand OA was studied by assessing localized BMD loss in the hands. The possible effect of anti-TNF α treatment on incident and progressive hand OA was examined by its effect on secondary hand OA in RA.

Generalized osteoporosis in recent-onset RA

Generalized osteoporosis is a well-known complication in patients with uncontrolled, longstanding RA with severe joint destruction, functional disability, and immobilization, resulting in a two-fold increase in risk of hip and vertebral fractures.[2] In order to unravel the common inflammatory mechanisms between generalized osteoporosis and joint destruction, osteoporosis data from just diagnosed patients with active, and anti-rheumatic treatment naïve RA were collected in a cross-sectional study. In **chapter 2** we show that osteoporosis, defined as T-score ≤ 2.5 SD, is found in 11%, 4%, and 9% in the hip and/or spine, in only the hip and, in only the spine, respectively, of the newly diagnosed, active, DMARD- and corticosteroid-naïve patients with RA. Besides well-known risk factors for generalized osteoporosis, such as postmenopausal status, low body mass index, and familial osteoporosis, the presence of rheumatoid factor, and longer duration of inflammatory symptoms are associated with osteoporosis and/or reduced BMD, indicating that generalized osteoporosis is an inflammation-driven process. However, still, in this very early, treatment-naïve, stage of the disease, the prevalence of osteoporosis in our postmenopausal RA patients is roughly comparable with the prevalence in two Dutch cohorts with postmenopausal women from the general population, emphasizing the importance of both early anti-inflammatory and anti-osteoporotic intervention, including stimulating physical activity, reducing risk of falls, and starting anti-osteoporotic medications in patients at high risk for fractures, in order to prevent high occurrence of osteoporosis and accelerated generalized BMD loss in RA.[3-5]

Generalized BMD loss in the first year of RA

Accelerated generalized BMD loss seems to be inflammation-driven in RA. The effect of different, modern, anti-rheumatic treatment strategies, including corticosteroids and the anti-TNF α infliximab, on generalized BMD over time is unknown. In **chapter 3** we demonstrate that BMD loss after 1 year is 1.0% and 0.8% of baseline BMD in the hip and spine, respectively. This is considerably higher than the BMD loss of around 0.5% after 2 years in the femoral neck in the general Dutch population above 55 years.[6] No significant differences in generalized BMD loss are observed between the treatment groups, including corticosteroids and infliximab, after 1 year of treatment, suggesting that the effect of these drugs on suppressing disease activity outweighs any negative effect on generalized bone metabolism. The use of calcium and/or vitamin D supplementation does not protect against generalized BMD loss, but the use of bisphosphonates does. Patients with more progressive destructive disease are more susceptible for accelerated BMD loss during the first year, independent of the allocated treatment group, emphasizing that erosions and generalized BMD loss share a common inflammation-driven pathway in RA.

Localized and generalized BMD loss in the first years of RA

It is thought that localized BMD in the proximity of inflamed joints is more prone to degradation due to inflammation than generalized BMD in the hip and spine where RA is less active. In **chapter 4** we confirm that there is significantly more localized BMD loss in the hands than generalized BMD loss in the hip and spine after 2 years of treatment (median loss 2.5% versus 0.5 to 1.0% after 2 years). While generalized BMD loss is after 2 years again not significantly different between the four treatment groups, localized BMD loss in the hands after 1 and 2 year(s) is significantly less in the initial combination groups due to earlier suppression of the inflammation during the first six months of the treatment (median localized BMD loss 3.6%, 3.3%, 1.4%, and 1.6% for group 1-4 after 2 years). There are no significant differences in localized BMD loss between initial combination therapy including quickly tapered high dose of prednisone and initial combination therapy including the TNF α inhibitor infliximab. This emphasizes that the anti-inflammatory effect of induction therapy with corticosteroids exceeds the direct catabolic effect of it on BMD, and that initial combination therapy with the anti-TNF α infliximab is not superior with regard to BMD loss to initial therapy including quickly tapered high dose of corticosteroids. Above all, early and intensive suppression of inflammation is crucial to prevent, especially localized, BMD loss. Underlining further the role of inflammation on BMD, both generalized and localized BMD loss are associated with progressive erosive damage in the joints. The use of oral bisphosphonates protects against generalized BMD loss, however, not against localized BMD loss. This indicates that oral alendronate 10 mg/day or 70 mg/week and risedronate 5 mg/day or 35 mg/week might be insufficient to protect localized BMD by too little counteraction of the high resorptive activity of osteoclasts originating in adjacent inflamed synovial tissue. Above all, in order to reduce and stop inflammation-driven localized BMD loss effectively, suppression of inflammation is essential.

Localized BMD gain in RA patients in remission

High inflammatory activity results in both joint damage progression and localized BMD loss. Adequate suppression of inflammation might result in a reversal of damage given the constant dynamics of bone formation and bone resorption. Repair of erosive damage in case of adequate suppression of inflammation is sometimes seen, and it is thought that gain in BMD is more often the case and easier detectable. We studied whether gain in localized BMD could be detected by the fully automatic and sensitive technique digital X-ray radiogrammetry (DXR). In **chapter 5** it is shown that RA patients in continuous clinical remission (DAS <1.6) during 1 year have, at group level, no BMD loss whereas patients with continuous low or high disease activity,

$1.6 \leq \text{DAS} \leq 2.4$ and $\text{DAS} < 2.4$, respectively, have significant BMD loss (0% versus 2% and 3%). At patient level, 35% of the patients in continuous remission have gain in BMD compared to only 11% and 6% of the patients with low and high disease activity. Moreover, patients with BMD gain show zero Sharp-vanderHeijde damage progression compared to 2 and 4 points in patients with stable BMD and BMD loss, respectively. These data again confirm that localized BMD in the hands is a dynamic marker resembling sensitively the current state of inflammatory activity in RA patients. It also suggests that remission, rather than low disease activity, is the optimal outcome at which to aim treatment decisions in patients with RA.

Localized BMD loss as predictor for destructive RA

Peri-articular and localized BMD loss is found in early phases of RA, before the stage of joint destruction, and even in the undifferentiated phase of the RA process.[7,8] In **chapter 6** we demonstrate the value of changes in localized BMD in the hands, measured by DXR, to predict subsequent joint destruction in early RA. In the first year, the sensitivity and negative predictive value of BMD loss in the hands for detecting progressive total joint damage are quite high, 87% and 93% respectively, whereas the specificity and positive predictive value are low, 36% and 23%, respectively. Localized BMD loss in the first year of RA predicts subsequent progressive joint damage in hands and feet after 4 years. However, joint damage progression in the first year is almost a ten-fold stronger predictor. It is possible that earlier BMD evaluation, for instance three to four months after disease onset or even in the undifferentiated phase of arthritis, might still be a useful tool to predict poor outcome in RA patients.

Inflammation and progressive hand OA

As shown in the previous chapters, localized BMD loss in the hands is a dynamic marker for inflammatory activity, and is associated with progressive joint destruction in RA. It is believed that systemic and local inflammatory activity also plays a role in pathogenesis of hand OA. In **chapter 7** this is investigated by studying the association between localized BMD loss in the hands and progression of radiographic hand OA over 2 years in the Genetics, ARthrosis and Progression (GARP) study. Accelerated BMD loss is twice more often present in progressive hand OA compared to non-progressive hand OA or no hand OA, suggesting that inflammation indeed plays a role in the etiology of progressive hand OA. This could indicate new targets for therapeutic interventions in hand OA.

Effect of anti-TNF α on progressive hand OA in RA

New treatment modalities for hand OA are highly needed because of the high prevalence, the substantial burden, and the completely lack of disease modifying drugs. TNF α inhibition might be a potential new target in hand OA.[9-11] **Chapter 8** addresses secondary radiographic hand OA progression in patients with RA treated in the BeSt study. In this RA population, 1 out of the 10 patients have incident secondary OA, and 1 out of the 3 patients progressive secondary OA in the interphalangeal joints of the hands over 3 years. High inflammatory activity, measured by high erythrocyte sedimentation rate and progressive erosive joint damage over 3 years, is associated with incident and progressive secondary OA in the distal interphalangeal joints. Patients receiving therapy with infliximab have reduced incident secondary OA in proximal interphalangeal joints, independent of the decrease in inflammation, suggesting that TNF α inhibition might be effective against secondary hand OA via other bone linked pathways than suppression of inflammation. Further research is needed to explore the effect of anti-TNF α treatment in primary hand OA.

Future perspectives

This thesis emphasizes that in recent-onset RA, localized BMD loss and, to a lesser extent, generalized BMD loss are inflammation-driven processes, and that therefore early and effective

remission induction therapy is necessary to stop BMD loss. While TNF α inhibitors might theoretically be preferable as bone-preserving anti-rheumatic treatment due to the possible bone building effect, this thesis underlines the importance of quick and effective suppression of inflammation, irrespective of the choice of the specific agents. Even combination therapy with corticosteroids, if given in a quickly tapered high dose, conserves BMD due to the strong anti-inflammatory effect. Nevertheless the conventional oral antiresorptive agents, especially bisphosphonates, are still necessary to prevent further generalized BMD loss, while they have no effect on localized BMD loss.

Since the abundance of osteoclast activity in contrast with osteoblast activity, mainly by the RANKL/OPG signaling pathway, seems to be responsible for both joint damage as well as generalized and localized BMD loss in RA, the current challenge is identifying therapeutic opportunities to treat all forms of bone loss at once. Direct intervention in this pathway by RANKL inhibition or OPG stimulation might stop or even repair articular and extra-articular bone damage. Recent clinical trials using denosumab, a humanized anti-RANKL antibody, showed even repair of RA joint damage, and reversal of localized and generalized BMD.[12,13] Furthermore, in animal studies treatment with OPG leads to the presence of osteoblasts, and extra bone formation, resulting in arrest, but not repair, of erosions and reversal of generalized BMD loss.[14,15] However, treatment with both denosumab and OPG does not result in decrease in inflammatory parameters, suggesting a bone-linked, and not a inflammation-linked pathway.[16,17]

Furthermore, enhancing osteoblast activity by stimulating the Wnt signaling pathway or suppressing the Wnt-inhibitor dickkopf-1 are potential molecular targets for prevention and treatment of articular and extra-articular bone involvement in RA.

Another way to target all forms of bone loss in RA is with potent bisphosphonates by their direct inhibitory effect on osteoclast activity. Zoledronic acid is a potent third-generation aminobisphosphonate that is thought to act by inhibiting osteoclast lifespan.[18] In animal studies zoledronic acid effectively suppressed structural joint damage, and localized bone loss, although there was no effect on clinical synovitis.[19,20] Studies investigating other bisphosphonates also confirm the positive effect of these agents on bone turnover, and the absence of an effect on clinical inflammation in RA.[21-23]

Randomized clinical trials are needed to explore the combined effect of anti-inflammatory drugs and agents targeting osteoclasts, directly, such as potent bisphosphonates, or via the RANKL/OPG or Wnt signaling pathway, on progression in erosive joint damage, localized and generalized BMD loss, fractures, and clinical parameters.

RA is a heterogeneous disease ranging from non-destructive disease responding to monotherapy to severe, destructive, and disabling disease refractory to multiple treatments. Therefore tailor-made treatment for the individual RA patient would diminish both undertreatment, leading to unnecessary bone destruction and dysfunctionality, and overtreatment, leading to unnecessary adverse events and costs. In spite of recent progress in the field of identifying predictors of destructive disease, such as the presence of autoantibodies and joint damage at the time of the diagnosis of the disease, there is need for more accurate tools that will allow early and accurate differentiation between aggressive and non-aggressive disease course. Localized BMD loss in the metacarpals measured by DXR seems a promising, sensitive, and non-invasive tool to predict rapid destructive disease, provided it detects BMD loss earlier than radiographs detect joint damage progression. However, after 1 year of follow-up, radiological joint damage progression, according to the by van der Heijde modified Sharp score, is a much stronger predictor of subsequent joint damage progression than BMD loss measured by DXR. Localized BMD loss during the first few months after diagnosis, or even in the undifferentiated phase of the RA process, might have a greater predictive value in clinical practice. Further studies are needed on

the predictive value of early localized BMD loss by DXR in RA or undifferentiated arthritis, and the additional value of it when incorporated in known predictive models.[24-26] Furthermore, novel biomarkers, that reflect the turnover and activity of the synovium, bone, and cartilage tissues, might improve these algorithms further.

In contrast with RA, in OA no disease modifying treatment exists. Local and systemic inflammation seems to be an important pathway in the etiology of hand OA. TNF α inhibition decreased the incidence of secondary hand OA in our RA population. The potential value of treatment with TNF α inhibitors, and other anti-inflammatory drugs, has to be investigated in clinical studies with patients with primary hand OA. Furthermore, since TNF α inhibition influenced secondary hand OA not by suppression of inflammatory activity, new bone-linked targets for therapeutic interventions in hand OA has to be explored.

Conclusions

Patients with recent-onset RA with high inflammatory activity have significant localized and, to a lesser extent, generalized BMD loss in the first years of their disease. Early and effective intervention with combination anti-rheumatic drugs, including prednisone or infliximab, results in less localized BMD loss in the hands. Conventional oral bisphosphonates protect against generalized BMD loss, however not against localized BMD loss, in RA. In patients in clinical remission, increase in localized BMD is frequently seen. Localized BMD loss in the hands in the first year of RA is predictive for subsequent joint damage, however not independent of progressive joint damage. Just as in RA, localized BMD loss in the hands is accelerated in progressive hand OA, emphasizing the role of inflammatory activity in primary hand OA. Treatment with TNF α inhibition decreases secondary hand joint progression in OA probably by direct influencing the bone metabolism.

Identifying therapeutic strategies and opportunities to treat or prevent all forms of bone loss and functional disability in RA and OA remains a challenge. Remission of disease in patients with RA and OA is the ultimate target.

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