the pooled effect of the bisphosphonates, the effect of 0.57 represents a 2.0% difference in the percent change in BMD between the two drugs in favour of bisphosphonates. A conversion of the pooled effect size was not performed for fluoride for the few studies considered, or for calcitonin, because there was no difference between the effect of calcitonin and that of vD.

**Conclusions:** vD plus calcium was found to be more effective than either no therapy or calcium alone in controlling BMD loss. The efficacy of vD was lower than that of bisphosphonates or fluoride (although only 2 trials were considered) but equivalent to that of calcitonin. Therefore, treatment with vD plus calcium, as a minimum, should be prescribed to patients on long-term corticosteroid treatment.

**Comment**
Steroid-induced osteoporosis is a problem that can largely be prevented by giving adequate (preventive) treatment. Unfortunately, only a limited number of patients who are treated with corticosteroids are treated sufficiently with well-known and well-proven therapies (1). This meta-analysis by S. Amin et al. evaluates the role of vitamin D alone or in combination with calcium in the management of corticosteroid-induced osteoporosis. It is quite clear that vitamin D in combination with calcium is effective in diminishing the loss of bone mineral density, and even (though not significantly) in reducing the number of fractures. However, there is one problem with the included studies: in most of these studies the vitamin D levels before the start of the study are not reported, and thus it is possible that the observed efficacy of vitamin D is partly due to the treatment of unrecognised hypovitaminosis D. Therefore, we cannot be completely sure that patients who are not deficient in vitamin D do indeed improve due to vitamin D treatment. However, vitamin D is inexpensive and well tolerated. In many countries the determination of vitamin D in serum costs as much as one year of treatment with vitamin D. No evidence has been supplied that active vitamin D is superior to normal vitamin D in this context; therefore consensus suggests using normal vitamin D supplementation.

It was to be expected that vitamin D, whether or not in combination with calcium, is less effective than bisphosphonates or fluoride in the prevention of bone mineral loss. The efficacy of calcitonin was comparable to the efficacy of vitamin D. The present guidelines should be: When patients are treated with glucocorticoids at a dosage of 7.5 mg or more daily for a prolonged period of time (expected to be 6 months or longer) additional treatment with calcium and vitamin D is necessary. This treatment should be combined with bisphosphonates in elderly patients and/or in patients with a BMD measurement that is lower than one standard deviation below the T-value (2).
nal MR images. An MRI score (0 to 18) was calculated. Conventional radiography of the hand and wrist was performed at months 0 and 12 after study inclusion. In the dominant wrist, the bases of metacarpals, the carpal bones, and the distal radius and ulna were assessed with respect to the presence or absence of bone erosions, scored from 0 to 15. Non-parametric methods, Kruskal-Wallis tests, and the Mann-Whitney tests were used to analyze differences between groups of pts, and the Wilcoxon-Pratt test was used to analyze changes within the single patient. An analysis of statistical correlation was performed by the Spearman test. Area under the curve (AUC) values of MRI-determined synovial membrane volumes, synovial membrane hypertrophy scores, and clinical and biochemical markers were calculated by the “trapezium method”.

Results: No significant difference was found between the randomization groups (only DMARDs and DMARDs plus prednisolone) with respect to progressive bone destruction by MRI and by radiography. Significant synovial membrane volume reductions were observed after 3 and 6 months in the DMARDs plus prednisolone group, and after 6 and 12 months in the DMARDs group (P < 0.01 - 0.2, by Wilcoxon-Pratt test). The erosive progression rate on MRI was highly correlated with baseline scores and, particularly, with AUC values for the synovial membrane volume (Spearman’s r = 0.69, P < 0.001), but not with baseline or AUC values for local or global clinical parameters. Erosive progression was found by MRI and/or conventional radiography in none of 5 wrists with baseline volumes < 5 cm³, but in 8 out of 10 wrists with baseline volumes > 10 cm³. That indicates a predictive value of baseline synovial membrane volumes at baseline. Wrist bone erosions were detected in 24 pts (138 bones) by MRI and in 14 pts by traditional radiography. MRI was more sensitive in revealing new erosions: at 1 year MRI revealed 22 new bones with erosive changes (10 wrists), while RX revealed 12 new bones with erosive changes (9 wrists).

Conclusions: The volume of synovial membranes determined by MRI provides detailed information about the RA joint inflammatory process and is highly correlated to the rate of progressive joint destruction. In RA, the evaluation of synovitis by MRI may be a valid method for the assessment of local inflammation and a predictor of the joint destructive process.

Comment

The assessment of RA is based on the core data set proposed at Maastricht (1993) and accepted by WHO, ILAR, ACR, and other groups (number of swollen joints, number of tender joints, patient’s assessment of pain, patient’s global assessment of disease activity, one laboratory evaluation of an acute-phase marker such as ESR and/or CRP, self-administered functional assessment). There has been considerable international standardisation of clinical assessment in RA, but clinical measurements remain an inexact science, while laboratory measurements of disease activity are weak predictors of the clinical course. Major advances have been made in the imaging of RA, the most important being the introduction of MR tomography. The value of different MR techniques in following the natural course of RA, defining clinical pathological inter-relationships, evaluating disease activity and therapeutic efficacy, and predicting the future development of destructive changes is currently under evaluation. Due to inherent high contrast soft tissue resolution and multiplanar capabilities, MRI demonstrates directly inflammatory synovial proliferation and its effects on all anatomical components of the joint.

Early MRI studies of RA were mainly dedicated to qualitative evaluation of the structural consequences of the joint disease (1). MRI has proved capable of demonstrating early synovitis, joint effusion, and cartilage and bone erosions with high sensitivity. Some MRI techniques, for example, signal rescaling on fat-suppressed T1-weighted images and magnetization-transfer techniques improve the contrast between the synovium, the joint effusion and other anatomical structures. In practice, the most common method of enhancing inflammatory synovial proliferation is i.v. administration of gadolinium containing paramagnetic MRI contrast agents (Gd-DTPA). Due to hyperemia and the increased vascular permeability of actively inflamed synovium and pannus, small molecular gadopentetic acid accumulates in the extracellular space, thereby permitting a qualitative distinction from fibrous non-active pannus and joint effusion.

Objective evaluation of disease activity requires quantification and measurements. A number of studies have been performed with the use of fast gradient-echo dynamic Gd-DTPA MRI aimed at quantifying the rate of synovial contrast enhancement (2). Synovial membrane uptake of Gd-DTPA is a time-related phenomenon dependent mainly on inflammatory tissue perfusion and microvascular permeability, both representing pathophysiological indicators of acute inflammation. Significant correlations between synovial membrane enhancement and histologic features of active inflammation have been demonstrated (3), but it is unclear whether peak enhancement or the rate of enhancement is of a greater significance. Some technical parameters, such as optimal slice selection for region-of-interest measurements, which should represent only the actively inflamed synovium and exclude joint fluid, as well as inappropriate temporal resolution, could invalidate the results of dynamic imaging. Nevertheless, dynamic MRI seems to enable the sensitive quantification of increased perfusion and microvascular permeability, which reflect the inflammatory activity of synovial proliferation and to be capable of assessing the response to different therapeutic regimes. The volume of joint effusion may indicate the severity of inflammatory rheumatic disease and reflect the effect of therapy. It has been proven that MRI with the use of 3D data obtained from heavily T2-weighted axial sections of the knee joint enables the accurate and precise quantification of joint fluid volume (4). However, a vital indicator of disease activity in RA is active inflammatory synovial proliferation. A number of studies have attempted to quantify the volume of synovial proliferation (5, 6). An appreciable heterogeneity of synovial proliferation, reflecting the degree of inflammatory activity, has been shown in different qualitative and dynamic MRI studies, not only between various joints, but even within a single small joint. Ideally, the most objective marker of disease activity should be the total volume of synovium with high inflamma-
tory activity. In practice, it is not possible to evaluate all of the inflamed joints nor to measure precisely only the actively inflamed synovium. A necessary compromise is therefore a measurement of the volume of inflamed synovium as large as possible, applied on the highest number of joints. The vast majority of MRI studies have been done on the knee, which may have a large amount of pannus, but which still represents only a single joint. In the present study (7) six regions within the wrist were included, which consequently better reflect the global inflammatory activity of the disease.

There is now increasing interest and familiarity with applications of MRI in RA. In spite of the great potential of this imaging method, a robust, relatively simple, reproducible and widely acceptable scoring system complementary to existing plain film radiographic scores has not yet been developed. The heterogeneity of MRI equipment and its rapid development makes standardisation difficult. The exact imaging protocol still widely differs therefore from centre to centre and often reflects the technical level of available MRI modalities. Several attempts have been made to establish a protocol. Rominger et al. (8) were the first to suggest a scoring MRI system. Østergaard et al. (7) proposed a relatively simple synovial membrane hypertrophy score, which can easily replace more time-consuming, purely quantitative measurements. A similar, but more sophisticated system was recently developed and validated (9). The drawback is that both systems include only the wrist. An eventual additional evaluation of the MCP and PIP joints, which are frequently involved in RA, would be more representative and better comparable to existing x-ray scoring systems.

The modern approach is early, aggressive, anti-rheumatic treatment of RA, which is vital to prevent long-term disability. The early identification of patients who are at risk of developing progressive disease on the basis of reliable prognostic markers is therefore of great practical importance. A search for MRI features related to the progression of articular destruction is currently developing. It has been shown that progression of bone destruction can be expected in joints in which an inflammatory active pannus is demonstrated by contrast-enhanced MRI (10). Østergaard et al. (7) proved that MRI-determined synovial membrane volume may be used as a predictor of progressive joint destruction. In the majority, but not all, of cross-sectional or longitudinal clinical studies, and irrespective of whether qualitative or quantitative MRI techniques are used, there is an appreciable disaccordance between MRI, clinical, laboratory and x-ray findings. Several explanations are possible, but many questions remain. Some objective clinical data seem to be insensitive. Self-reported symptoms and health status information differ among patients and could have a cultural basis. Laboratory markers reflect global disease activity in RA, while MRI are performed on a limited number of joints. Conventional radiography has traditionally been used as the “gold standard” to measure the severity and progression of RA, mainly through the assessment of erosive bone changes. However, radiography lacks sensitivity to early manifestations of RA and to change during the course of the disease. The fact that some MRI findings do not translate into x-ray lesions raises the question of the uniform pathogenesis and the end result of synovitis in RA.

The development of MR is far from complete. With ultra-fast imaging on higher field scanners, novel imaging sequences and dedicated coils, macromolecular and other new contrast agents, and in vivo spectroscopy, MR will continue to play an important role in research and clinical practice.

References