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Perspectives of combined treatment strategies in osteoporosis

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J. D. Ringe

PERSPECTIVES OF COMBINED TREATMENT STRATEGIES IN OSTEOPOROSIS

The large number of highly effective drugs that have been approved for prevention and therapy of osteoporosis allows today a therapeutic strategy adapted to the individual case. This therapeutic strategy, however, must be based on a clear diagnosis taking into account age, sex, risk factors of lifestyle, underlying diseases, activity and severeness of osteoporosis etc. of the individual patient. Table 1 gives an overview on the therapeutic options for the management of established postmenopausal osteoporosis.

Generally accepted as a first step of therapy (basic treatment) is calcium/vitamin D supplementation. The second step comprises analgesic therapy, physiotherapy and increase of physical activity according to the needs and possibilities of the patient. The third step is Bone Turnover Modifying Therapy (BTMT), i.e., a long-term drug therapy modifying the activity of osteoblasts, osteoclasts or both with the aim to increase bone mass and mechanical strength and to avoid future fractures. The worldwide dominating BTMT of today is antiresorptive therapy (e.g., HRT, SERMs, calcitonin, bisphosphonates).

There is only a small number of drugs with proven or potential osteoanabolic effect (e.g., fluoride, strontium, PTH). The highly specific stimulatory effect of fluoride on osteoblasts is generally accepted, but its fracture reducing potency is still discussed controversially. Accordingly sodium fluoride (NaF) or monofluoro-phosphate (MFP) are only approved for therapy in few countries. For the near future strontium may be an interesting candidate as an uncoupling agent showing both antiresorptive and osteoanabolic properties. An interesting question for today is however, whether a combination of osteoanabolic and antiresorptive substances has additive effects on bone mineral density (BMD), clinical outcome and fracture rate.

In comparison to the large studies with antiresorptive monotherapy only some small studies using combined regimens have been performed so far. These include as osteoanabolic agents fluoride and parathyroid hormone and as antiresorptive drugs HRT, calcitonin and etidronate. All studies report encouraging results.

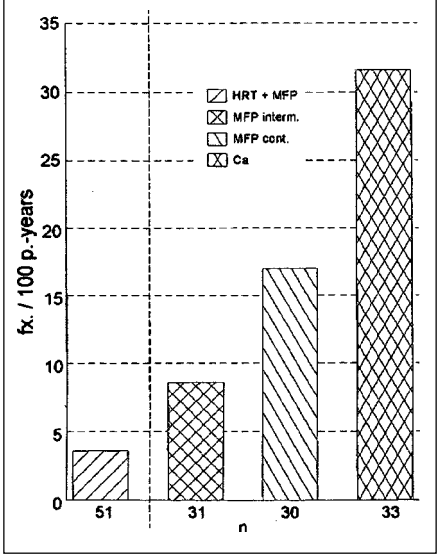
A prospective placebo-controlled study from the group of Christiansen proved a synergistic effect of HRT and MFP in the prevention of postmenopausal osteoporosis. The authors observed a significant decrease in bone resorption without changing of bone formation and underlined the positive effects on both trabecular and cortical bone mass [1].

The objective of our own study was to assess whether a combination with antiresorptive HRT is able to improve the therapeutic results of MFP/calcium therapy in established osteoporosis. As a supplement to a previous 3-arm trial [2] we performed an observational one-arm study on 60 postmenopausal women treated intermittently 3 months on 1 month off with low dose MFP (= 15 mg F/day) plus continuously 1000 mg calcium and oral or transdermal HRT for three years. The earlier groups had been treated with either the same low dose intermittent fluoride plus calcium regimen, or higher dose (20 mg) continuous fluoride plus calcium, or calcium alone. The combination was safe and well tolerated. There was a significant reduction in back pain. After 3 years spinal BMD had increased by 15.3 % and at the femoral neck by 3.5 % (annual rates +5.1 and +1.2 % respectively). These increase rates ranged between those of the lower and

Table 1: Treatment of established postmenopausal osteoporosis

1. **Basic therapy**
   Recommendations to avoid individual risk factors, supplementation of calcium/vitamin D
2. **Analgesic therapay**
   Analgetic drugs, physiotherapy
3. **Bone-turnover-modifying therapy**
   a. Antiresorptive medications (HRT, raloxifen, calcitonin, bisphosphonates)
   b. Osteoanabolic medications (fluoride, strontium, PTH, statins?)
   c. Combinations (e.g. fluoride plus HRT)

Figure 1: Comparison of vertebral fracture rates between patients treated with fluoride plus HRT, two different regimens and calcium alone (cf. text)



the higher fluoride-dose groups of the former study. We observed 5 patients with new vertebral fractures, i.e., 3.0 fractures/100 patient-years. The respective vertebral fracture rates for 15 mg MFP intermittently without HRT was 8.6, for 20 mg MFP continuously was 17.0 and for calcium alone was 31.6 (fig. 1).

We conclude from this own study that the combined therapy with MFP/calcium and HRT restores BMD very effectively at the spine and moderately at the proximal femur. The incidence of new vertebral fractures was significantly lower in all three fluoride groups in comparison to calcium monotherapy. The lowest rate however was observed with the combined MFP/Ca/HRT regimen [3].

These data are encouraging to study other combined regimens, e.g., fluoride-SERMs or fluoride-bisphosphonates.

In a pilot study on 23 postmenopausal women with severe established osteoporosis we examined the effectiveness of a combined antiresorptive-osteoanabolic regimen (EFCaD = Etidronate, Fluoride, Calcium, vitamin D) in comparison to a pure antiresorptive treatment (ECaD = Etidronate, Calcium vitamin D) in restoring the highly reduced bone mass. In the combined regimen we applied etidronate 400 mg/day for 14 days followed by 76 days with 20 mg fluoride, 1200 mg calcium and 800 I.U. vitamin D daily. Already after 12 months we found a highly significant additive effect in the group receiving the combined therapy. Bone mineral density increased in the EFCaD-group at the lumbar spine and femoral neck with +11.5 % and +4.4 % respectively, while in the ECaD-group the corresponding rates were only +2.3 % and +0.6 %.

The literature on combined antiresorptive-osteoanabolic therapy of osteoporosis is still small and the existing data are not sufficient to give distinct recommendations. The so far existing data, however, are very interesting. It is suggested that the bone forming potency of fluoride can be further increased by combining with an antiresorptive agent and that the quality of the newly formed bone tissue may be improved.

Prof. Dr. med. Johann Ringe

Johann Ringe is Head of the Department of Internal Medicine at Leverkusen Hospital, University of Cologne, Germany. He originally studied medicine at the Universities of Göttingen, Montpellier, and Heidelberg, between 1966–1972, and completed his doctoral thesis at the German Centre of Cancer Research in Heidelberg in 1971. From 1973–1979 he trained in general internal medicine at the University Hospital of Hamburg-Eppendorf where he was involved in research into calcium metabolism and bone diseases. In 1985, following specialization in osteology and rheumatology, the Medical Faculty of the University of Hamburg nominated Professor Ringe for Professor of Internal Medicine. He then took up his current position in 1988.

Professor Ringe is a member of numerous national and international societies including the German Societies of Internal Medicine, Endocrinology, Rheumatology and Geriatrics, the American Society for Bone and Mineral Research and the Scientific Advisory Board of the European Foundation for Osteoporosis. He is also a member of GREES (Group for the Respect of Ethics and Excellence in Science)

The author of over 400 scientific publications, Professor Ringe is involved in clinical studies on estrogen, selective estrogen receptor modulators (SERMS), fluoride, vitamin D metabolites and bisphosphonates in the treatment of osteoporosis. He is also involved in clinical studies on male and corticosteroid-induced osteoporosis.

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