Evidence-based Rheumatology

edited by M. Matucci Cerinic

ACE inhibitors could prevent long-term renal damage in systemic sclerosis patients experiencing scleroderma renal crisis

Authors: V.D. Steen and T. Medsger
Title: Long term outcome of scleroderma renal crisis
Source: *Ann Intern Med* 2000; 133: 600-3

Aim

The outcome of scleroderma renal crisis, a once fatal complication of systemic sclerosis (SSc), has dramatically improved with angiotensin-converting enzymes (ACE) inhibitors, even if its long-term outcomes are not known. A prospective, observational cohort study was undertaken to investigate the short- and long-term outcomes, natural history, and risk factors in patients (pts) with SSc and scleroderma renal crisis.

Methods

The 145/807 pts with diffuse SSc (dSSc) seen at Pittsburgh University in the period 1979-1996, who experienced renal crisis and received ACE inhibitors were examined. The remaining 662 dSSc pts who had never experienced scleroderma renal crisis served as controls. Demographic data and follow-up clinical and laboratory data obtained at regular intervals were compared to identify risk factors for the 4 specific outcomes studied, which were: no dialysis (pts not requiring dialysis in the first year after treatment) and temporary dialysis (pts who received dialysis and later discontinued it for at least 1 year), both considered as good outcomes; permanent dialysis (pts who required permanent dialysis) and early death (pts who died within 6 months of renal crisis), both considered as poor outcomes. The methods and complications of dialysis were also analyzed and the frequency of dialysis complications was compared to the frequency reported in the literature for other dialysis recipients. The prospective follow-up period was 5-10 years.

Results

61% of the SSc pts who experienced renal crisis and received ACE inhibitors had a good outcome: 55 of them (38%) never received dialysis, and 34 (23%) underwent temporary dialysis (discontinued after a mean of 8 months). Only 4 of these pts (4%) progressed to chronic renal failure and permanent dialysis. All the pts with a good outcome continued to take ACE inhibitors, although one non-compliant pt later had to resume dialysis. Survival in the good outcome group was similar to the 662 dSSc pts who had never experienced scleroderma renal crisis.

39% of the pts had a poor outcome. 32 (19%) underwent permanent dialysis (4 from the good outcome group and 28 from the permanent dialysis group). Nine of them had peritoneal dialysis and 23 hemodialysis. Six pts underwent kidney transplant. Only 75% of the pts who received permanent dialysis continued ACE inhibitors while receiving dialysis. 28 pts (19%) died early (a mean of 3 months after the renal crisis). 64% of these pts required dialysis. Pts who died early were more frequently male, had more prominent myocardial disease, were significantly older and had a higher initial serum creatinine concentration, compared the pts in the other groups. Death was most frequently due to multi-organ failure, infections and problems with dialysis. SSc pts undergoing dialysis experienced dialysis-related problems similar to those of other pts on dialysis for renal failure due to causes other than SSc.

Conclusions

ACE inhibitors are both effective in managing scleroderma renal crisis in dSSc pts and in decreasing the need for dialysis. For this reason, therapy should be promptly and aggressively started as soon as a scleroderma renal crisis is diagnosed and indefinitely continued if there is any chance for additional improvement in kidney function in SSc pts.

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Comment

Scleroderma renal crisis – a potential success story

A decade ago I published a review on renal scleroderma (1) in which Table 2 showed the till then published reports on the prevalence of scleroderma renal crisis (SRC). The figures varied between 2.6% and 15% of all cases of scleroderma. The Pittsburgh group then reported 108 out of their 1068 (1) cases. In the present report covering at total of 807 cases, observed in the period 1979-1996, the prevalence is given as 145 or 18%. Since there is no evidence of an increasing relative prevalence of SRC, one must assume a selection mechanism, and this points to a weakness in this otherwise valuable

report. In other words, the conclusions apply to the presented population of patients,and generalisations could be misleading. For instance, severe renal involvement seems to be rare in the black population in South Africa (2). There is, however, little doubt about the main message in Dr. Steen's report regarding the value of early aggressive treatment with ACE inhibitors, which have improved the long term outcome substantially, even among patients with advanced renal insufficiency. A survey of 332 such patients in 1990 showed only a 36% 3-year survival rate. Rheumatologists as well as dermatologists and other physicians seeing patients with suspected or established scleroderma have a great responsibility in recognising the earliest signs of severe renal involvement. Aggressive therapy, mainly with ACE inhibitors,does change the course and save lives. Whether all patients should be instructed to self-monitor their blood pressure may need some qualification. Also, the most severe form of SRC is not hypertensive (1). But the kidneys in a majority of all scleroderma patients suffer from impaired functional reserve, which is why over treatment is unlikely (4).

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Daily injections of parathyroid hormone increase bone mineral density and reduce the risk of vertebral and non-vertebral fractures in post-menopausal women

Authors: R.M. Neer *et al.*

Title: Effect of parathyroid hormone (1-34) on fractures and bone mineral density in post-menoupasal women with osteoporosis

Source: *N Engl J Me*d 2001; 344: 1434-41

Aim

Daily subcutaneous injections of parathyroid hormone or its aminoterminal segments have potent anabolic effects on bone without inducing hypercalcemia. In order to assess the effects of recombinant human PTH 1-34 on BMD and on vertebral and non-vertebral fractures, a multicenter, randomized, double-blind, placebo controlled trial was conducted. The study was stopped earlier than planned due to the decision of the sponsor.

Methods

1,637 post-menopausal ambulatory women with at least one moderate or two mild atraumatic vertebral fractures at screening, who had entered menopause at least 5 years before the beginning of the study, were enrolled at 99 centers in 17 countries. For women with fewer than two moderate fractures, an additional criterion was hip or spine bone mineral density (BMD) at least 1.0 SD below the T score.

All women received daily supplements of 1 g calcium and 400 to 1200 UI vitamin D and were randomly assigned to self-administered daily subcutaneous injections of placebo (544 women), or 20 mg (541 women) or 40 mg (552 women) of PTH 1-34. Serum calcium before and 4 to 6 hours after the injection and 24-hour calcium and creatinine excretion were measured at baseline and after 1, 6, 12 and 24 months of treatment. If the post-injection serum calcium was high or if urinary calcium exceeded 350 mg per day, and if the increase persisted, the calcium supplement was stopped permanently or the volume of the study drug was halved until the abnormality disappeared.

All women underwent radiography of the thoracic and lumbar spine at the baseline and at the end of the study. Each vertebra was graded as normal, or mildly, moderately or severely deformed and new vertebral fractures were registered. Non-vertebral fractures were documented by review of radiographs and classified as fragility fractures if not caused by an efficient trauma.

Lumbar BMD was measured in all women at baseline, at 12 and 18 months, and at the end of the study; proximal femoral BMD was measured in all women at baseline, at 12 months and at the end of the study. Forearm and total body BMD were assessed in a group of women at baseline, at 12 months and at the end of the study. Height was measured at baseline and every 12 months. Blood counts, serum chemical tests and urinalysis were performed at baseline and at 1,6,12, and 24 months. Serum antibodies to PTH 1-34 were performed at baseline and at 3, 12 and 24 months.

Results

The mean duration of study treatment in the groups receiving placebo, PTH 1-34 20 mg and 40 mg was 18 ± 5, 18 ± 6 and 17 ± 6 months, respectively.

Baseline and follow-up radiographs were available in 1327/1637 women (81%). In 105 of them, one or more new vertebral fractures occurred. With respect to placebo, PTH 1-34 20 mg and 40 mg reduced the risk of one or more vertebral fractures by 65% and 69%, respectively. The relative risks of fracture in the 20 mg and 40 mg were 0.35 and 0.31, respectively compared to the placebo group (95% confidence intervals, 0.22 to 0.55 and 0.19 to 0.50). The mean loss in height was greater in the placebo group than in the 20 mg and 40 mg PTH 1-34 groups ($p = 0.002$).

Both total new non-vertebral fractures and new non-vertebral fragility fractures occurred more in the placebo group than in the 20 mg and 40 mg PTH 1-34 groups ($P < 0.05$ in all cases). New non-vertebral fractures were found in a total of 119 women. Fifty-three (10%) had a fracture in the placebo group, 34 (6%), and 32 (6%) in the 20 mg and 40 mg PTH 1-34