Medroxyprogesterone acetate with Zoladex™ for long-term treatment of fibroids: effects on bone density and patient acceptability

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A randomized trial was carried out to investigate the effect of 12 months administration of the gonadotrophin-releasing hormone agonist (GnRHa) Zoladex™ in combination with either placebo or medroxyprogesterone acetate (MPA) from the third month. Bone density, markers of bone resorption, symptoms and uterine volume were monitored in 24 women with symptomatic fibroids or menstrual problems. A total of 21 women were recruited to act as controls for the assessment of bone parameters. Vasomotor side-effects were reduced significantly in the MPA-treated group. The reduction in uterine volume in women with fibroids was not impaired by the addition of MPA. The bone markers osteocalcin and alkaline phosphatase were assessed in plasma, and the cross-links pyridinoline and deoxypyridinoline measured in urine. Changes in these markers are reported which suggest increases in bone resorption during the period of observation. Bone mineral density (BMD) was assessed by dual energy X-ray absorptiometry at the spine and forearm. The net reduction in BMD at the spine in the treated groups was 4.30 ± 0.59% at 6 months and 7.50 ± 0.78% at 1 year, with no change in the control group. No change was seen in forearm BMD. No protective effect was observed when MPA was added. At 1 year after the completion of treatment, BMD remained significantly below baseline, and this has implications for the prolonged use of GnRHAs.

Key words: bone/bone density/fibroids/GnRH agonist/medroxyprogesterone acetate

Introduction

Sex hormone-dependent gynaecological conditions, including endometriosis, menorrhagia and uterine leiomyomata (fibroids), are increasingly managed by the suppression of cyclical ovarian activity using gonadotrophin-releasing hormone agonists (GnRHa). This allows the sustained inhibition of pituitary gonadotrophins with a reduction in gonadal steroid output. Single s.c. injections of goserelin acetate (Zoladex), 3.6 mg depot, have been shown to result in post-menopausal oestradiol concentrations and amenorrhoea (West and Baird, 1987).

However, there is concern about the long-term use of these agents because it has been shown that a reduction in bone density occurs (Johansen et al., 1988). In addition, users effectively experience a pseudo-menopause associated with unwanted side-effects, such as vasomotor symptoms and vaginal atrophy. The use of ‘add-back’ therapies, such as hormone replacement therapy or progestogens, may reduce these unwanted effects without reducing efficacy (West et al., 1992). Mandel et al. (1982) have shown that medroxyprogesterone acetate (MPA) may inhibit bone resorption. We were interested to add this to the Zoladex treatment to observe its effect on bone mineral density (BMD) and the cross-links pyridinoline (PYD) and deoxypyridinoline (DPD), valid markers of collagen degradation. West et al. (1992) reported that adding MPA at the start of therapy prevents the rapid reduction in uterine volume required for the treatment of fibroids, but that its introduction after 3 months of gonadal suppression by Zoladex does not interfere with further fibroid shrinkage. This study also showed that the suppression of luteinizing hormone, follicle stimulating hormone and oestadiol was maintained when progestogens were added.

We designed a study to observe changes in bone density and metabolism in a randomized placebo-controlled trial conducted over 12 months, comparing the effect of the GnRHa Zoladex™ (3.6 mg goserelin acetate; Zeneca Pharmaceuticals, Macclesfield, UK) in women with symptomatic fibroids and/or menorrhagia, with sequential MPA or a placebo ‘added back’ at 3 months. The subjects and 21 age-matched controls were followed up for 1 year after the Zoladex depots were discontinued.

Materials and methods

Pre-menopausal women who wished to avoid surgical treatment for symptomatic fibroids or menstrual problems were recruited from the outpatient department of Edinburgh Royal Infirmary (Edinburgh, UK), where a full gynaecological assessment had been made. The presence of fibroids was confirmed by ultrasound. Women who had conditions affecting bone metabolism or who had taken any hormonal agent within the past 3 months were excluded from the study. Women whose initial BMD (Z score) was >1.6 SD below age-matched controls were also excluded from the study. Once the women had given informed consent in writing, they were randomized to receive sequential therapy with either Zoladex plus placebo or Zoladex plus MPA. The Zoladex depot was injected s.c. into the lower anterior abdominal wall using a pre-packed syringe. Treatment was initiated on days 2–5 of the menstrual cycle and given every 28 days thereafter. After the first 3 months and at the time of administration of the
fourth implant, adjunctive therapy in the form of MPA, 15 mg daily, or a placebo was commenced. The actual treatment given to individual patients was determined by a random scheme prepared by the Biometrics Group, Zeneca Pharmaceuticals. The randomization was held in the hospital pharmacy. In all, 12 depots were given to each of the subjects. Full approval for the study was obtained from the Lothian Health Board Paediatrics/Reproductive Medicine Ethics of Medical Research Sub-Committee (Edinburgh, UK).

On admission to the study, a full history was taken and an examination performed. An endometrial biopsy was taken when considered to be indicated clinically. Height and weight were measured. A blood sample was obtained on entry to the study to exclude renal dysfunction and conditions affecting bone turnover. All subjects completed a daily diary chart throughout the study, in which menstrual bleeding, dysmenorrhoea, breast discomfort, abdominal bloating, irritability, depression, hot flushes and night sweats were recorded individually. Symptom severity was assessed semi-quantitatively on a four-point scale using a visual system of shading in individual boxes. Diaries were collected and reissued at each monthly visit.

Bone turnover was assessed pretreatment, after 24 and 48 weeks of treatment and at 24 weeks after the completion of treatment, by measuring plasma calcium, alkaline phosphatase and osteocalcin. Urine was collected for the markers of collagen degradation: PYD and DPD. Calcium and alkaline phosphatase were measured using a SMAC 2 analyser (Technicon). Osteocalcin was measured in plasma using an in-house radioimmunoassay developed in the Department of Clinical Chemistry at the Royal Infirmary of Edinburgh (Edinburgh, UK). The method uses antiserum raised in rabbits against bovine osteocalcin. Tracer (125I-labelled osteocalcin) and the standards were prepared against bovine osteocalcin. The antiserum cross-reacted with human osteocalcin and was used to measure osteocalcin in plasma. The assays were performed in batches for each study. The intra-assay variation was 4.5% and the interassay variation was 12.1%. Urine samples were analysed for creatinine, PYD and DPD using solid-phase extraction and reversed-phase high-performance liquid chromatography after acid hydrolysis, as described by Pratt et al. (1992). A fully automated method was used which has improved the reproducibility of the technique [coefficient of variation (CV) <3%]. Analyses were performed at the Rowett Research Institute, Aberdeen, UK. The results are expressed relative to the urinary creatinine concentration (nmol/mmol creatinine).

BMD was measured by dual energy X-ray absorptiometry using a Hologic QDR 1000W densitometer (Hologic Inc., Waltham, USA). BMD was measured at the lumbar spine (L1–L4) and the ultradistal forearm. Measurements were made pretreatment and at 24, 48, 72 and 96 weeks. This system is described in detail by Wahner et al. (1988). Measurement of a spine phantom was performed daily and the long-term precision was excellent (the mean BMD was 1.0384 g/cm² with a SD of 0.0054 and a CV of 0.52%). Short-term in-vivo precision (duplicate measurements of 12 subjects with repositioning between scans) was measured and the CV at the lumbar spine was 0.80% and at the forearm was 0.46%.

Uterine volume was monitored at 12 week intervals using real-time ultrasound expressed as the mean percentage change from the baseline value as described previously (West et al., 1987).

Power calculations were made based on an earlier pilot study of the effect of Zoladex on bone density and the appropriate number of subjects recruited to detect significant changes in bone density. All analyses were conducted on an intention-to-treat principle (all patients receiving the treatment to which they were allocated). For the analysis of symptom diaries, total monthly scores were calculated for each symptom in each subject. Statistical comparisons between the demo-
Figure 1. Severity of hot flushes (lower figure) and night sweats (upper figure) during the study period expressed as the mean (±SEM) of total 4 weekly scores.

Figure 2. Change in bone mineral density (mean ± SEM) at the lumbar spine during and 1 year after the completion of treatment.

Figure 3. Urinary concentration of the cross-links deoxypyridinoline (DPD; upper figure) and pyridinoline (PYD; lower figure) during the study period. Results are expressed in nmol/mmol creatinine. **P < 0.01; *P < 0.05 versus baseline.

Biochemical parameters

The results of the cross-links PYD and DPD are shown in Figure 3. Results are expressed as nmol/mmol creatinine. At baseline there was a highly significant variability between subjects in the overall mean baseline level (P < 0.0001), and within subjects there was a significant difference between the five time points in each group (P < 0.0001). The nature of these differences was examined using t-test comparisons. There was found to be no difference between the rates of either bone loss or bone increase after treatment was discontinued in either group. Apparently MPA offered no protective effect. There was no obvious relationship between the percentage change in BMD and body weight, pretreatment BMD or age. By 1 year after treatment was discontinued, spine BMD remained 5.3% (placebo group) and 4.5% (MPA group) below that measured before treatment, and this still represented a highly significant reduction (P < 0.001). The study design did not include measurements beyond that time. The rate of bone loss at the ultradistal forearm during treatment was no different than at baseline and was within the reproducibility of the machine. There was no significant change in BMD at either the spine or forearm in the control group. This is as we would expect in pre-menopausal women.

Bone density

Changes in BMD at the lumbar spine are shown in Figure 2. There was no difference in BMD at the lumbar spine between either of the treatment groups or the controls at baseline. At baseline there was a highly significant variability between subjects in the overall mean baseline level (P < 0.0001), and within subjects there was a significant difference between the five time points in each group (P < 0.0001). The nature of these differences was examined using t-test comparisons. There was found to be no difference between the rates of either bone loss or bone increase after treatment was discontinued in either group. Apparently MPA offered no protective effect. There was no obvious relationship between the percentage change in BMD and body weight, pretreatment BMD or age. By 1 year after treatment was discontinued, spine BMD remained 5.3% (placebo group) and 4.5% (MPA group) below that measured before treatment, and this still represented a highly significant reduction (P < 0.001). The study design did not include measurements beyond that time. The rate of bone loss at the ultradistal forearm during treatment was no different than at baseline and was within the reproducibility of the machine. There was no significant change in BMD at either the spine or forearm in the control group. This is as we would expect in pre-menopausal women.

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MPA with Zoladex™ for long-term fibroid treatment

Figure 4. Plasma osteocalcin (µg/l) (upper figure) and plasma alkaline phosphatase (IU/l) (lower figure) during the study period. ***P < 0.001; **P < 0.01; *P < 0.05 versus baseline.

Figure 3. There was no difference in the rate of change of DPD excretion between the placebo and MPA groups. PYD excretion did not change significantly in the MPA-treated group. It can be seen that excretion of PYD and DPD peaks at 48 weeks (at the end of active treatment) and falls thereafter. The cross-links at this time remain higher than at baseline and were not measured beyond this time point. No relationship was found between the rate of bone loss and cross-link excretion at any time point. In the control group there was no difference in cross-link excretion throughout the study period.

There was no change in plasma calcium throughout the study period. The alkaline phosphatase and osteocalcin results are shown in Figure 4. Alkaline phosphatase increased similarly in both the placebo and MPA groups, and the nature of these differences from baseline is shown in Figure 4. Plasma osteocalcin paralleled these increases, and these highly significant increases were observed in each group. There was no change in any of these parameters in the control group.

Uterine response

Uterine response was expressed in terms of the mean percentage change in volume, taking the pretreatment baseline measurement for each woman as 100% (Figure 5). There was a sustained reduction in uterine volume during therapy which did not differ between the two groups, with gradual regrowth of the fibroids over the 12 months following its cessation. Two women (both with fibroids; one from each group) had hysterectomies during the 12 month follow-up period, and six subsequently required surgical treatment of their fibroids during the 2 years after cessation of treatment. They were equally distributed between the two treatment groups.

Discussion

In a previous pilot study (West et al., 1992) we reported that the use of MPA as an adjunct to Zoladex reduces vasomotor side-effects without impairing the uterine or clinical response to the GnRHa. This has now been confirmed in the present randomized study, which also illustrates that a further reduction in uterine size can be induced by more prolonged use of the agonist. However, we have failed to confirm the hypothesis that adjunctive use of MPA delays uterine fibroid regrowth following the cessation of therapy. Indeed Carr et al. (1993) have suggested that progestagens may have a trophic effect. The duration of follow-up after the pilot study was only 6 months; at 6 months the results of the present study show a similar delay in uterine regrowth, which may be related to the delay in the return of ovarian function, and was not sustained at 12 months. Our finding that only 80% of the subjects achieved amenorrhoea during therapy is similar to that of other studies using GnRHa alone.

Zoladex therapy results in a steady reduction in BMD at the lumbar spine. Adjunctive therapy with the progestogen MPA does not prevent the bone loss associated with GnRHa, in this case Zoladex. The beneficial effects of MPA on bone metabolism were suggested by Mandel et al. (1982) following the finding that a reduction in urinary excretion of calcium and hydroxyproline was seen in post-menopausal women on 20 mg MPA daily. However, bone mass was not measured in that study. In contrast, Gallagher et al. (1991) found that MPA failed to prevent post-menopausal bone loss as assessed by the direct measurement of spinal and radial bone density. Friedman (1989) observed radial bone density (using single photon absorptiometry) in 16 women who were receiving the agonist in addition to 20 mg MPA or placebo. Bone loss was not observed in either group; however, this is not unexpected because only cortical bone was observed.

The fall in circulating oestrogen in the first treatment cycle may initiate bone loss. The rate of decline in BMD is no different in the period from pretreatment to 6 months, and that from 6 to 12 months. The net reduction in BMD at the spine in the treatment groups was 4.30 ± 0.59% at 6 months and 7.50 ± 0.78% at 1 year, similar to that seen by Bianchi et al. (1995). Progesterone receptors are known to be present on osteoblasts, but are only found in the presence of oestrogen (Eriksen et al., 1988). Thus the inability of MPA to protect bone may be because of the absence of progesterone receptors in hypo-oestrogenic states. These rates of bone loss at 6 months are similar to those seen during breastfeeding (equivalent loss 4.9 ± 1.5%), a physiological hypo-oestrogenic state (Caird et al., 1994).

The use of other agents has been explored with a view to protecting against loss of bone mineral while on GnRHa therapy. Cyclical oestrogen/progestogen therapy has been...
shown to be bone sparing by Friedman (1989) and Maheux et al. (1991), who added adjunctive therapy at 3 months, as in this study. Leather and Studd (1992) noted that bone loss was prevented when hormone replacement therapy was commenced at the time of the first implant in sufferers of premenstrual syndrome. In their study no change in BMD was seen in hormone replacement therapy users, while a bone loss of 4.8% in 6 months was seen in the Zoladex-alone group, which is similar to the bone loss found here. No data are available concerning the effect of the synthetic steroid Tibolone (Livial; Organon) in association with GnRHa on bone mineral or fibroids. However, Tibolone does prevent post-menopausal bone loss (Lindsay et al., 1980).

The elevation in alkaline phosphatase and osteocalcin seen at 6 and 12 months in the treatment groups would suggest an increase in bone turnover during Zoladex therapy. This was paralleled by an increased excetration of the cross-links PYD and DPD. By 24 weeks after the treatment was discontinued none of these markers of bone activity had returned to normal, suggesting a continuing increase in bone turnover. However, osteocalcin remained relatively higher than the cross-links compared with baseline, suggesting increased bone formation at this time as BMD was in fact increasing. The above findings are in agreement with those of Scharla et al. (1990), who found an increase in alkaline phosphatase and phosphate in women treated with Zoladex alone. It was suggested that this simply reflected enhanced bone turnover. These results are similar to those reported by others for the use of a GnRHa alone (Johansen et al., 1988; Waibel-Treber et al., 1989).

In summary, this study confirms that a significant loss of bone mineral occurs with Zoladex therapy. This loss is similar to that seen during breastfeeding, which is a physiological situation. In addition, biochemical changes suggesting altered skeletal metabolism do occur. The changes in bone mass at the spine are not prevented with adjunctive progestogen therapy (MPA). This is in contrast to its already proven symptomatic benefits (West et al., 1992). A more useful alternative may be the addition of conventional hormone replacement therapy, and Maheux et al. (1991) have shown that low-dose oestrogen and sequential progestrone may protect against bone loss with no apparent increase in the growth of fibroids.

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