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The effects of post-surgical administration of goserelin plus anastrozole compared to goserelin alone in patients with severe endometriosis: a prospective randomized trial

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BACKGROUND: Among patients using GnRH analogues for endometriosis it has been postulated that peripheral and inflammation-induced in-situ aromatization of adrenal androgens are probably the main reasons for the high rates of failure during follow-up. We hypothesized that in cases with premenopausal severe endometriosis, use of a combination of anastrozole and goserelin to achieve almost maximal endocrine blockade of estrogen synthesis after conservative surgery may increase the pain-free interval and reduce the recurrence rates as compared to goserelin alone. METHODS: In a prospective randomized trial, we evaluated the efficacy of using either a combination of anastrozole and goserelin for 6 months or goserelin alone for 6 months after conservative surgery for severe endometriosis. The primary outcome measures were the symptom recurrence rates and the impact of treatment on endometriosis-related multidimensional score. The secondary outcome measures were the impact of allocated treatment regimens on menopausal quality of life and on lumbar spine bone mineral density (BMD). RESULTS: When we analyzed the Kaplan–Meier survival curves, we detected a statistically significant advantage of goserelin plus anastrozole as compared to goserelin only, in terms of the median time to detect symptom recurrence (>2.4 versus 1.7 months; log-rank test; $P = 0.0089$). This statistically significant advantage occurred with a relative risk of 4.3 [95% confidence interval (CI) 1.3–9.8]. Three cases out of 40 recurred in the goserelin plus anastrozole arm (7.5%), whereas we detected recurrences in 14 cases out of 40 cases in the goserelin-only arm (35%) during the follow-up period of 24 months. Based on these data, the interpretation of Kaplan–Meier curves indicates that at the end of follow-up, 54.7 versus 10.4%, respectively, of the patients were free of recurrence. The mean of the differences in terms of Δbaseline–24 months post-medical therapy multidimensional score were statistically significant in favour of goserelin and anastrozole (9.2 ± 2.1 versus 6.7 ± 2.8; paired *t*-test; $P < 0.0001$; 95% CI 1.5–4.0). We observed a statistically significant difference in suppression of estradiol concentrations and a significantly greater BMD loss at the end of treatment in the goserelin and anastrozole arm as compared to goserelin-only arm. However, this did not elicit deterioration in menopausal quality of life and the observed bone loss was not significant in terms of ΔBMD between the groups at 2 years of treatment withdrawal. CONCLUSIONS: Six months of treatment with anastrozole and goserelin as compared to goserelin alone increased the pain-free interval and decreased symptom recurrence rates in patients following surgery for severe endometriosis. Furthermore, menopausal quality of life and BMD at 2 years after medical therapy remained unaffected

Key words: anastrozole/endometriosis/goserelin

Introduction

Even though yet to be determined, it is recommended that post-operative adjuvant treatment should be instituted in order to minimize the risk of recurrence and to extend the pain-free period after conservative surgery in cases of severe endometriosis (American College of Obstetrics and Gynecology, 1999; Gambone *et al*., 2002). For this purpose, treatment with GnRH analogues for 6 months as post-surgical medical treatment has been the preference of the last decade (Vercellini *et al*., 1998). The desired treatment of the current decade is more targeted to endometriotic foci either by surgery and/or by locally acting medications in conjunction with ovarian blockade (Jones and Sutton, 2001; Vignali *et al*., 2002).

Recently, the molecular basis for the local treatment of endometriosis using an aromatase inhibitor has been discussed (Bulun *et al*., 1998, 1999, 2001, 2001; Takayama *et al*., 1998;

Zeitoun *et al*., 1999). According to these authors, the existence of two additional extraovarian sources of endogenous estrogen is probably an important reason for the high rate of failures during follow-up among patients using GnRH analogues. The first source is the peripheral aromatization of adrenal androgens and the second is the inflammation-induced aromatization in the endometriotic foci itself. GnRH analogues are ineffective in both of these estrogen production sites. Aromatase inhibitors are not able to inhibit ovarian function in premenopausal women and thus they are not able to create the desired almost complete hypoestrogenic milieu. The authors postulated that the addition of aromatase inhibitors to GnRH analogues in premenopausal patients could increase the disease-free interval by inhibiting both the ovarian and abovementioned two important extraovarian sources of estradiol (E_2).

Given this background, to test the clinical significance of this new hypothesis related to the two-drug adjuvant regimen, we conducted a prospective randomized study. We tried to answer the question whether anastrozole (Arimidex 1 mg; Astra-Zeneca, Macclesfield, UK), a third-generation aromatase inhibitor, in conjunction with the GnRH analogue goserelin (Zoladex 3.6 mg; Astra-Zeneca) could lower the recurrence rates and thus extend the symptom-free interval with acceptable morbidity as compared to goserelin alone after conservative surgery in severe endometriosis cases.

Materials and methods

Participants

This post-surgical medical therapy trial was undertaken between December 1998 and March 2003 among patients with severe baseline endometriosis (rASRM score >40) according to the American Society for Reproductive Medicine (American Society for Reproductive Medicine, 1997). All patients were surgically treated by a conservative approach between December 1998 and September 2000. This trial was conducted after the approval of the ethics committee of the institution and all subjects gave written informed consent to the trial protocol.

Interventions

In patients with a clinical suspicion of severe endometriosis, baseline grading of symptoms and physical findings was performed before the surgery according to the previously developed and widely used multidimensional scale (Biberoglu and Behrman, 1981). In this scale, symptoms of dysmenorrhoea, dysparenuia and pelvic pain were each scored by the patient, and the physical findings of pelvic tenderness and indurations were each scored by the physician as: none (0 point), minimal (1 point), moderate (2 points) or severe (3 points). The sum of these variables compromised the Total Pelvic Symptom Score (TPSS). In this trial, TPSS is considered to be the subjective clinical indicator of the disease severity at baseline and during the follow-up period of the study. After grading the TPSS as the sum of the symptoms and physical findings, all patients were subjected to diagnostic laparoscopy. Laparoscopy with histological proof was the ultimate tool to diagnose endometriosis at baseline. Laparoscopy is also considered to be the objective clinical indicator of disease severity and it was programmed in the luteal phase of the cycle. Among patients who had rASRM scores >40, the diagnosis of severe endometriosis was made and we attempted a thorough conservative surgery either by laparoscopy or laparotomy.

After the thorough conservative surgery, patients were considered eligible for the post-surgical medical therapy trial. Exclusion criteria included further desire for childbearing, any treatment for endometriosis within the previous 3 months, any concomitant disease that can be an established cause of chronic pelvic pain (inflammation sequela, myoma, pelvic congestion, adenomyosis, etc.), osteopenia or osteoporosis at bone mineral density (BMD) measurements according to the World Health Organization (1994) and any concomitant disease that can be a contraindication to goserelin or anastrozole.

In all patients, we prescribed 600 mg elemental Ca and 400 IU vitamin D (b.i.d.) in a commercially available medication (Cal D Vita; Roche, Basel, Switzerland). The first group of patients received anastrozole 1 mg/day plus s.c. depot injections of 3.6 mg goserelin every 4 weeks for 24 weeks with the first injection given in the first late luteal week of the menstrual cycle before discharge. The second group of patients received a placebo tablet in addition to the abovementioned goserelin regimen for 24 weeks. Patients were evaluated at 24 weeks of medical treatment, and at 6, 12, 18 and 24 months after the end of medical treatment.

Objectives and outcomes

The main objective of this trial was to assess the clinical efficacy of anastrozole in conjunction with goserelin as compared to goserelin alone in the adjuvant setting. Thus the primary outcome measures of this trial were (i) the recurrence rate and (ii) the impact of allocated treatments on TPSS during the follow-up period of 24 months after the end of medical treatment.

During this trial, recurrence was defined as symptoms and physical findings suggesting endometriosis with a TPSS of $\geqslant 7$ that requires alternative treatment at any time during the follow-up period of 24 months after the end of post-surgical medical treatment. Laparoscopy to diagnose recurrent endometriosis was not considered to be necessary in accordance with the recent literature (Hornstein *et al*., 1997; American College of Obstetrics and Gynecology, 1999; Ling, 1999; Vercellini *et al*., 1999; Winkel, 2000; Gambone *et al*., 2002). Thorough history taking, complete physical and detailed pelvic examination, transvaginal sonography, urinalysis, complete blood count, and endocervical examination to rule out chlamydia and gonococcus were performed to rule out pain syndromes other than endometriosis. The time to initiate alternative treatment was recorded for each patient. Examinations to detect recurrences were scheduled either by the request of the patient (whenever the patients had complaints, they were immediately examined to detect recurrences) or at the time of scheduled follow-up examinations at the immediate end of post-surgical medical treatment (24 weeks exam), and at 6, 12, 18 and 24 months post-surgical medical treatment. Symptoms of TPSS recorded by the patients (dysmenorrhoea, dysparenuia, pelvic pain) were studied as TPSS-Patient (TPSS-P). In each exam, TPSS was re-evaluated by the surgeons and noted for statistical analysis, and the probability of recurrence noted. During the study period we were able to record TPSS at baseline, at 24 weeks post-surgical medical treatment, and at 6, 12, 18 and 24 months post-surgical medical treatment. Whenever a recurrence was detected (TPSS $\geqslant 7$), we offered GnRH analogue plus add-back or definitive surgery as second-line treatments.

The secondary outcome measures of this trial were established to evaluate the adverse effects of therapy and were studied in two aspects. The first secondary outcome measure is the impact of treatment on the menopausal quality of life according to the 24-week examination findings and E_2 levels throughout the therapy. In order to assess the severity of climacteric symptoms as a measure of quality of life induced by the drug regimens, the modified Greene scale and Blatt–Kupperman Index were used (Greene, 1998; Alder, 1998). The

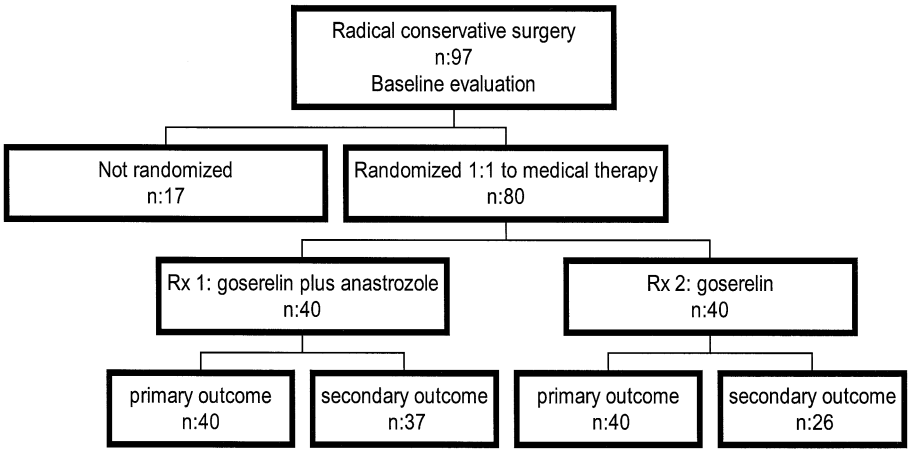

Figure 1. Diagrammatic flow of participants in the randomized post-surgical therapy trial of goserelin versus goserelin plus anastrozole.

validity and sensitivity of these scales have been established in climacteric research. These classification systems, though simple, construct a comprehensive measure of the multi-faceted and wide ranging symptom picture presented by the climacteric women. The modified Greene scale was used to determine the severity of vasomotor, somatic, psychological symptoms (anxiety and depression) and loss of sexual interest (Greene, 1998). The Blatt–Kupperman Index, in contrast, does not assess sexual interest, but vasomotor symptoms are of prime importance in this scale (Alder, 1998). All patients were instructed to self record the scales at 24 weeks of evaluation during the post-surgical medical treatment. The scales were reviewed and scored by a blinded psychiatrist. In order to assess the impact of treatment regimens on E_2 concentrations, blood samples were taken before the second, fourth and sixth goserelin administrations, and free E_2 levels were measured.

The second secondary outcome measure is the impact of medical treatment on L1–L4 vertebra BMD at 24 weeks of medical therapy and 24 months post-surgical medical treatment. Variables were studied at baseline, at 24 weeks of post-surgical medical treatment and at the end of the study period, i.e. 24 months after the post-surgical medical treatment. The BMD of the lumbar vertebra (L1–L4) were measured by dual-energy X-ray absorptiometry with the use of Hologic QRD (Hologic, Waltham, MA). The coefficient of variation of the machine over the study period was 3.5%.

Sample size calculation

In calculating the sample size required, the primary assessment was the recurrence rates. A 31% recurrence rate after laparoscopic reductive surgery and post-surgical treatment with a GnRH analogue has been reported (Hornstein *et al*., 1997). We expected a decrease in recurrence rates after laparoscopic conservative surgery and post-surgical treatment with anastrozole plus goserelin. A difference of 25% between the allocated treatments was considered significant. To have a 90% chance of detecting such a difference at an overall significance level of 5%, 40 patients for each group were required.

Randomization process and masking

Treatment allocation was performed in accordance with a computer-generated randomization sequence using numbered, opaque, sealed envelopes. The research assistants prescribed the drugs. Neither the surgeons nor the patients were aware of the regimen prescribed during the evaluation of TPSS recurrence during the study period. Randomization code was broken and unblinding occurred at the time of the diagnosis of recurrence.

Statistical methods

StatMate and Prism Software for Windows (Graph Pad) were used in the randomization process, sample size calculation and statistical analysis of this trial.

All raw data were tested to confirm the Gaussian distribution using the Kolmogorov–Smirnov test. The cumulative proportion of recurrences by plotting percent recurrences as a function of time was estimated by the method of Kaplan and Meier. The survival curves for each allocated treatment were compared with the log-rank test. The impact of treatment on TPSS as a primary outcome measure is studied in the efficacy-evaluable population; in order to mitigate the bias that would result from the missing data, we carried out the 'last observation carried forward procedure'. In this procedure, a patient's last measured response is applied to the subsequent scheduled observations for which data are not available and included in the statistical analysis (Archer and Pickar, 2002). Thus, for example, the TPSS of a patient with recurrence at 17 months is studied in the 18 months scheduled examination. In order to quantify the impact of treatment arms on TPSS during the study period, the non-parametric repeated measures ANOVA (Friedman test) with Dunn as the post-test was used. The differences of treatment effects on TPSS were assessed by the paired *t*-test and Wilcoxon matched-pairs signed-rank test. In the statistical analysis of the secondary outcome variables, intention-to-treat analysis (Archer and Pickar, 2002) was used; thus, it included the dropouts for whom data are not available at 24 months after post-surgical medical treatment. $P < 0.05$ was considered statistically significant.

Results

Participant flow, recruitment and baseline data

Ninety-seven women treated with conservative surgery between December 1998 and September 2000 for baseline severe endometriosis were considered eligible for the post-surgical medical treatment trial. Seventeen of them were excluded—eight patients refused randomization (five of them were treated by goserelin and anastrozole, three of them were by goserelin), in six patients osteopenia or osteoporosis was detected (they were treated by goserelin and weekly alendronate) and three patients chose not to receive treatment, but instead just to be monitored. The remaining 80 subjects were randomized and were followed for at least 24 months after the

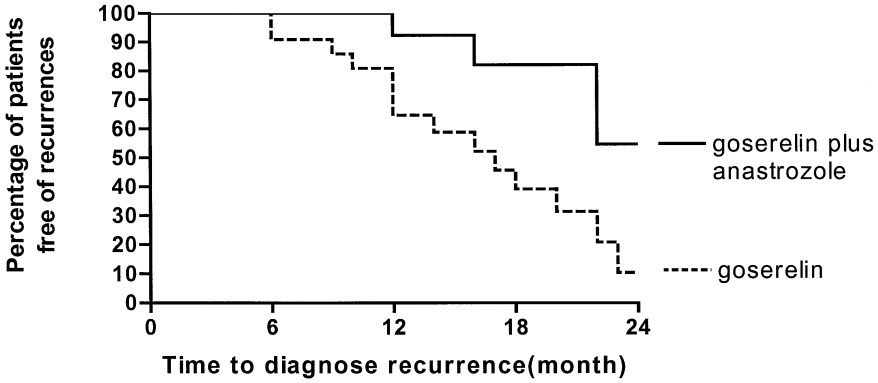

Figure 2. Kaplan–Meier curves for patients treated with goserelin versus goserelin plus anastrozole.

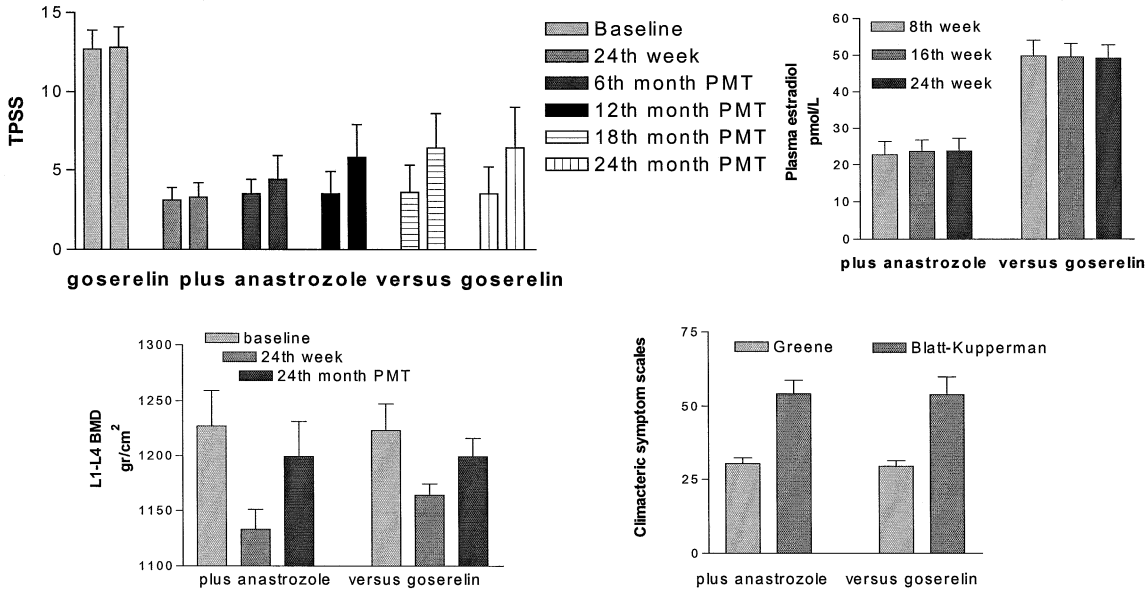

Figure 3. The impact of treatment arms on TPSS, plasma E_2, climacteric quality of life and BMD. *Post-medical therapy.

Table I. Baseline demographic and clinical characteristics of each group (mean ± SD)

	Goserelin plus anastrozole	Goserelin
Age	31.3 (±5.7)	32.4 (±6.1)
Body mass index	23.6 (±1.47)	24.5 (±1.31)
Gravidity	2.50 (±0.9)	2.57 (±0.9)
rASRM scores	61.2 (±14.2)	63.2 (±13.3)
Baseline TPSS[a]	12.7 (±1.2)	12.8 (±1.3)
Baseline TPSS-P[b]	7.8 (±0.9)	7.9 (±0.8)
L1–L4 BMD (g/cm^2)	1085 (±34.3)	1088 (±26.4)

[a]Total pelvic symptom score.
[b]The sum of dysmenorrhoea, dysparenuia and pelvic pain.

post-surgical medical treatment of 6 months. None of the randomized subjects were lost during the study period and for no patient violations of the study protocol occurred. The diagrammatic flow of the participants is given in Figure 1. The baseline demographic and clinical characteristics of each group are given in Table I. The baseline variables were statistically similar in each group.

Analysis: outcome and estimation

The survival curves obtained for the treatment arms are plotted in Figure 2. When we analyzed the Kaplan–Meier survival curves, we detected a statistically significant advantage in favour of goserelin plus anastrozole as compared to goserelin only, in terms of the median time to detect symptom recurrence (>24 versus 17 months; log-rank test; P = 0.0089). This statistically significant advantage occurred with a relative risk (RR) of 4.3 [95% confidence interval (CI) 1.3–9.8]. Three cases out of 40 recurred in the goserelin plus anastrozole arm (7.5%), whereas we detected recurrences in 14 cases out of 40 cases in the goserelin-only arm (35%) during the follow-up period of 24 months. Based on these data, the interpretation of Kaplan–Meier curves indicates that at the end of follow-up, 54.7 versus 10.4%, respectively, of the patients were free of recurrence.

In this trial, both treatment protocols proved to be statistically effective in reducing the TPSS during the study period (Figure 3). The comparisons of the impact of allocated treatments in terms of TPSS and 'TPSS-P' between the two

Table II. The impact of post-surgical medical treatment on TPSS and TPSS-P (mean ± SD)

	Goserelin plus anastrozole	Goserelin	*P* value (95% CI)
TPSS			
TPSS baseline	12.7 (±1.2)	12.8 (±1.3)	0.72[a] (–0.4 to 0.6)
TPSS at 24 weeks	3.1 (±0.8)	3.3 (±0.9)	0.40[a] (–3.4 to 1.4)
TPSS 6 months PMT	3.5 (±0.9)	4.4 (±1.5)	<0.001[b] (0.3–1.5)
TPSS 12 months PMT	3.5 (±1.4)	5.8 (±2.1)	<0.0001[a] (1.3–3.2)
TPSS 18 months PMT	3.6 (±1.7)	6.4 (±2.2)	<0.0001[a] (1.8–3.7)
TPSS 24 months PMT	3.5 (±1.7)	6.4 (±2.6)	<0.0001[a] (1.8–3.9)
TPSS-P			
TPSS-P baseline	7.8 (±0.9)	7.9 (±0.8)	0.61[a] (–0.2 to 0.4)
TPSS-P at 24 weeks	2.2 (±0.7)	2.2 (±0.6)	0.89[b] (–0.3 to 0.2)
TPSS-P 24 months PMT	2.8 (±0.7)	4.6 (±0.8)	<0.0001[b] (1.4–2.2)

[a]Paired *t*-test.
[b]Wilcoxon matched-pairs signed-rank test.

Table III. The impact of post-surgical medical treatment on ΔTPSS and on ΔTPSS-P (mean ± SD)

	Goserelin plus anastrozole	Goserelin	*P* value (95% CI)
ΔTPSS			
ΔTPSS baseline–24 weeks	9.6 (±1.5)	9.5 (±1.8)	0.88[a] (–0.7 to 0.6)
ΔTPSS baseline–24 months PMT	9.2 (±2.1)	6.7 (±2.8)	<0.0001[a] (1.5–4.0)
ΔTPSS-P			
ΔTPSS-P baseline–24 weeks	5.6 (±1.1)	5.7 (±1.1)	0.9[b] (–0.4 to 0.6)
ΔTPSS-P baseline–24 months PMT	5.0 ((±1.3)	3.3 (±1.2)	<0.0001[a] (1.1–2.3)

[a]Paired *t*-test.
[b]Wilcoxon matched-pairs signed-rank test.

Table IV. The impact of treatment regimens on specific symptoms' verbal rating scores (dysmenorrhoea, dysparenuia and pelvic pain) at 24 week of medical therapy (MT) and at 24 months PMT (mean ± SD)

	Goserelin plus anastrozole	Goserelin	*P* value (95% CI)[a]
Dysmenorrhoea			
Baseline	2.7 (±0.5)	2.6 (±0.6)	0.42 (–0.3 to 0.1)
24 weeks of MT	0.9 (±0.5)	1.1 (±0.5)	0.33 (–0.1 to 0.4)
24 months PMT	1.4 (±0.5)	1.7 (±0.7)	<0.05 (0.03 to 0.6)
ΔBaseline–24 weeks	1.7 (±0.8)	1.5 (±0.8)	0.29 (–0.6 to 0.1)
ΔBaseline–24 months	1.3 (±0.7)	0.8 (±0.9)	<0.05 (–0.8 to –0.04)
Dysparenuia			
Baseline	2.6 (±0.6)	2.6 (±0.5)	0.71 (–0.2 to 0.3)
24 weeks of MT	0.52 (±0.5)	0.50 (±0.5)	0.82 (–0.2 to 0.2)
24 months PMT	0.6 (±0.5)	1.4 (±0.8)	<0.0001 (0.4 to 1.0)
ΔBaseline–24 weeks	2.1 (±0.7)	2.1 (±0.8)	0.54 (–0.3 to 0.4)
ΔBaseline–24 months	1.9 (±0.8)	1.2 (±1.0)	<0.001 (–1.0 to –0.2)
Pelvic Pain			
Baseline	2.6 (±0.7)	2.7 (±0.5)	0.41 (–0.1 to 0.3)
24 weeks of MT	0.7 (±0.6)	0.6 (±0.5)	0.24 (–0.3 to 0.07)
24 months PMT	0.7 (±0.5)	1.5 (±0.5)	<0.0001 (0.5 to 1.0)
ΔBaseline–24 weeks	1.8 (±1.0)	2.0 (±0.7)	0.13 (–0.07 to 0.5)
ΔBaseline–24 months	1.8 (±0.9)	1.1 (±0.6)	<0.001 (–1.1 to –0.3)

[a]Wilcoxon matched-pairs signed-ranks test.

regimens are given in Table II The mean of the differences between the groups in terms of TPSS either at baseline or at 24 weeks of evaluation are not statistically significant. The mean/median of the differences between treatment regimens at 6, 12, 18 and 24 months post-treatment evaluation is statistically significant in favour of goserelin and anastrozole. The effect of allocated treatments in terms of ΔTPSS and of ΔTPSS-P is given in Table III. We were unable to detect a significant difference in terms of ΔTPSS (baseline–24 weeks evaluation) and ΔTPSS-P (baseline–24 weeks evaluation) between the allocated treatment arms. However, we detected a statistically significant difference in terms of ΔTPSS and ΔTPSS-P at 24 months post-treatment evaluation in favour of goserelin and anastrozole.

We also tested the impact of treatment regimens on specific symptoms as components of TPSS (Table IV). We detected a statistically significant difference in favour of goserelin plus anastrozole in terms of each symptom score and in terms of ΔBaseline–24 months post-medical therapy (PMT) scores of each symptom.

Furthermore, we tested the treatment arms in terms of their capacity to maintain their efficacy over the time frame of the

Table V. The impact of allocated treatment on secondary outcome measures

	Goserelin plus anastrozole	Goserelin	*P* value[a] (95% CI)
Plasma E_2 (pmol/l) 8 weeks	22.7 (±3.6)	49.8 (±4.3)	<0.0001 (25–28)
Plasma E_2 (pmol/l) 16 weeks	23.6 (±3.1)	49.5 (±3.7)	<0.0001 (24–27)
Plasma E_2 (pmol/l) 24 weeks	23.7 (±3.5)	49.1 (±3.7)	<0.0001 (23–27)
Greene scale score	30.3 (±1.9)	29.5 (±1.9)	0.20 (–1.5 to 0.3)
Blatt–Kuppermann score	54.1 (±4.7)	53.9 (±6.0)	0.90 (–2.5 to 2.2)
Δ L1–L4 BMD 24 weeks	93.8 (±33.2)	60.2 (±28.2)	0.003 (–50.5 to –16.7)
Δ L1–L4 BMD 24 months	27.1 (±46.3)	25.2 (±28.9)	0.46 (–16.9 to 36.4)

[a]Paired *t*-test.

study. The results of the non-parametric repeated measures ANOVA (Friedman test with Dunn's multiple comparisons test as the post-test) for each group indicates that in both groups when compared to baseline TPSS, the variation among column medians during the follow-up is significantly greater than expected by chance ($P < 0.0001$). In the goserelin and anastrozole regimen from 24 weeks on, the variation among column medians was not significantly greater than expected by chance ($P = 0.675$) during the remaining follow-up period, indicating the maintenance of efficacy (Figure 3). However, this was not the case in the goserelin arm—we were able to detect a statistically significant variation among column medians at 24 weeks versus 18 months post-treatment [rank sum difference (RSD) –82, $P < 0.01$], at 24 weeks versus 24 months post-treatment (RSD –76; $P < 0.001$) and at 6 versus 12 months post-treatment (RDS –31.5; $P < 0.001$) during the follow-up period. This indicates a stepwise increase of TPSS in the goserelin arm within the time frame of the study (Figure 3).

Adverse events

The impact of treatment regimens on E_2 levels and on climacteric symptoms as a measure of quality of life during the treatment period is given in Figure 3. In the repeated measures, one-way ANOVA test done separately for each group, we do not have evidence that free E_2 concentrations differed through the therapy period ($P = 0.69$ for goserelin; $P = 0.47$ for goserelin plus anastrozole). However, goserelin plus anastrozole lowered E_2 concentrations significantly as compared to the goserelin-only regimen (Table V). In contrast, the mean of the differences between the treatment regimens either in terms of modified Greene scale scores or the Blatt–Kupperman index scores as a measure of menopausal quality of life at 24 weeks of evaluation are not statistically significant (Table IV).

We noted that patients in the goserelin plus anastrozole arm lost 7.7% of their baseline L1–L4 BMD at 24 weeks evaluation and 2.3% of their baseline L1–L4 BMD at 24 months of treatment withdrawal. The representative BMD losses in the goserelin arm were 4.9 and 2.1%, respectively (Figure 3). These losses were statistically significant either at 24 weeks of evaluation or at 24 months of treatment withdrawal (Table V). Then, we compared the ΔBMD measurements between groups in order to compare the allocated treatments. We found a statistically significantly greater bone loss in the goserelin plus anastrozole arm at 24 weeks of evaluation (Table IV). However, we noted no statistically significant differences between the allocated treatments in the mean of the Δbaseline–24 months post-surgical medical treatment (Table V).

Discussion

Endometriosis, as it still recurs after currently recommended therapy, requires, more than ever, fully integrated medical and surgical management, and an ongoing dialogue with laboratory scientists. Keeping this in mind, we would like to discuss (i) the rationale of our adjunctive regimens we have chosen in this trial, (ii) the impact of anastrozole in conjunction with goserelin on recurrence rates and on chronic pelvic symptoms and signs of endometriosis, and (iii) the side-effects of the double-drug adjuvant regimen in comparison to goserelin.

In a significant proportion of patients, the pain related to endometriosis eventually returns. One explanation for the observed long-term inefficiency of GnRH analogues is the presence of significant E_2 production that continues in the adipose tissue, skin and endometriotic foci *per se* during the GnRH analogue treatment. Inflammation-induced aromatization in the endometriotic foci itself represents the intra-acrine mechanism of estrogen action in endometriosis. The prostaglandin E_2 content, the aberrant expression of aromatase, the presence of 17β HSD Type 1 and the absence of 17β HDS Type 2 collectively raise the local levels of E_2 of the ectopic endometrial tissues. Furthermore, GnRH analogues are ineffective to stop peripheral aromatization of androstenedione in adipose tissue and skin fibroblasts; therefore, there is an ongoing peripheral supply of estrone and E_2 to the target foci that are rich in 17β HSD Type 1 (Takayama *et al*., 1998; Bulun *et al*., 1998, 1999, 2000, 2001; Zeitoun *et al*., 1999; Vignali *et al*., 2002).

In this trial we did not include a placebo group because it seemed unethical to us given the proven effectiveness of GnRH analogues and current practice (Vercellini *et al*., 1998; American College of Obstetrics and Gynecology, 1999; Winkel, 1999; Jones and Sutton, 2001; Gambone *et al*., 2002; Vignali *et al*., 2002). Therefore, we have chosen goserelin as the standard arm of the trial. We intended to increase the hypoestrogenism by the double-drug regimen both centrally and peripherally. Aromatase inhibitors given alone are not able to completely inhibit ovarian steroidogenesis (Vignali *et al*., 2002), and, furthermore, may increase follicular recruitment (Mitwally and Casper, 2001) and may lead to ovarian stimulation and cyst formation. Given alone they are only sufficiently potent to block extraovarian estrogen pro-

duction (Dowsett, 1999; Santen and Harvey, 1999; Vignali *et al*., 2002). However, in the presence of a GnRH analogue which itself results in ovarian inhibition, aromatase inhibitors are effective to achieve near maximal estrogen suppression (Dowsett, 1999; Santen and Harvey, 1999). Therefore, in this trial we tested the efficacy of anastrozole in the presence of ovarian inhibition and did not have an anastrozole-only group.

In the experimental arm of this trial, goserelin was used in order to inhibit ovarian steroidogenesis, and anastrozole to inhibit the consequences of peripheral aromatization and the aberrant expression of aromatase in the endometriotic foci.

When we analyzed the Kaplan–Meier survival curves, we detected a statistically significant advantage in favour of goserelin plus anastrozole as compared to goserelin only, in terms of the median time to detect symptom recurrence (>24 versus 17 months; log-rank test; $P = 0.0089$). This statistically significant advantage occurred with an RR of 4.3 (95% CI 1.3–9.8). Three cases out of 40 recurred (TPSS >7) in the goserelin plus anastrozole arm (7.5%), whereas we detected recurrences in 14 cases out of 40 cases in the goserelin-only arm (35%) during the follow-up period of 24 months. Based on these data, the interpretation of Kaplan–Meier curves indicates that at the end of follow-up, 54.7 versus 10.4%, respectively, of patients were free of recurrence. The median time to detect recurrence in the goserelin treatment arm was 17 months post-treatment. In contrast, the median time to detect recurrence in the goserelin and anastrozole arm was >24 months.

In this trial both treatment protocols proved to be statistically effective in reducing the TPSS; however, we observed a more profound, stable and long-lasting effect of goserelin and anastrozole on TPSS during the study period. Furthermore, the impact of treatment in terms of TPSS and individual symptom score reduction was statistically relevant in favour of goserelin and anastrozole. Based on our data, we argue that almost complete targeted endocrine blockade of estrogen biosynthesis in the adjuvant setting after conservative surgery involving goserelin and anastrozole is superior to the standard approach. This novel approach was associated with a lower rate of recurrence and better, continuous symptom control within the time frame of the study.

The most common adverse effects of GnRH analogues are associated with hypo-estrogenism. Our data clearly demonstrates that anastrozole is a very effective suppressant of E_2 concentration even in the presence of the GnRH analogue goserelin. However, it was interesting to note that this combination was tolerated as well as goserelin only in the context of the climacteric quality of life. The mean of the differences between the treatment regimens either in terms of modified Greene scale or the Blatt–Kupperman index scores as measures of climacteric quality of life were not statistically significant. The explanation for this unexpected finding may be our sample size, which is relatively small to study the differences in quality of life or the inefficiency of the armamentarium available today to detect differences in the menopausal quality of life below a threshold value of E_2 or the biological suppression we have detected is not of clinical relevance. Even though not studied in our population, it may also be related to the dynamics of sex hormone-binding globulin and free testosterone in the presence of goserelin and anastrozole, as it theoretically leads to an increase in free testosterone indices.

To our knowledge the impact of double-drug regimen to BMD of women with endometriosis has not been reported in the literature. Both regimens had significant detrimental impact on BMD even after treatment withdrawal. The observed BMD loss was statistically more pronounced at 24 weeks of evaluation in the goserelin plus anastrozole arm. Even though the bone loss did not recover at 24 months of evaluation, none of our patients were osteopenic or osteoporotic according to WHO criteria either at 24 weeks or at 24 months of post-surgical medical treatment evaluation. In our opinion this finding is very important from the clinical standpoint, because for women with no history of fragility fracture, only WHO definitions of osteopenia and osteoporosis are associated with a high risk of fracture (American Association of Clinical Endocrinologists, 2001). Furthermore, the physiological bone loss of 0.5% per year that is evident after the third decade should also be taken into account (Stevenson *et al*., 1989). Our statistical results point to a significant loss of BMD in L2–L4 at 24 weeks and 24 months of evaluation within each treatment arm; however, the size of the bone loss being significant in favour of goserelin at the end of treatment is not significant at 2 years after treatment. The masking of bone loss with bisphosphonates may be considered; however, this has not been studied in our patients.

In our local practice the costs of a 6-month treatment with goserelin plus anastrozole and goserelin are around US$2500 and 1250, respectively. Even though measuring the cost-effectiveness is beyond the scope of this trial, in the era of managed care medicine the costs of our drugs must be interpreted cautiously with regard to the limited costs and efficacy of their alternatives, particularly progestins with or without estrogens (Vercellini *et al*., 2003).

In conclusion, we showed that in patients with severe endometriosis after conservative surgery, almost maximal endocrine blockade of estrogen synthesis achieved with anastrozole and goserelin for 6 months as a post-surgical medical treatment is a rational treatment. On the basis of the presented findings, this combination in the adjuvant setting increases the pain-free interval, decreases recurrence rates, and improves symptom control without further deteriorating the menopausal quality of life and bone metabolism. In our opinion, key targets for future development in the treatment of severe endometriosis are (i) further assessment of the potential role of aromatase inhibition in premenopausal patients, (ii) strategies to enhance the degree of hormone suppression for prolonged periods without deteriorating the bone, (iii) investigation of the optimal sequential use of different compounds such as estrogens/progestogens, immunomodulators and anti-inflammatory agents in addition to GnRH analogues and aromatase inhibitors.

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