Adjuvant oestrogen therapy does not improve disease activity in postmenopausal patients with rheumatoid arthritis

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Abstract

Objective To investigate whether oestrogens can be used as treatment to diminish disease activity in women with rheumatoid arthritis.

Methods—Forty postmenopausal female patients with active rheumatoid arthritis participated in a placebo-controlled, double-blind study on the possible beneficial effect of adjuvant treatment of oestradiol on disease activity.

Results—Thirty three patients completed 52 weeks of treatment with 2 mg oestradiolvalerate or placebo. No statistically significant difference was found in and between both treatment groups with regard to articular indices, pain score by visual analogue scale, erythrocyte sedimentation rate and health questionnaire on daily activities before, during and at the end of the study.

Conclusion—This first randomised prospective placebo-controlled study shows no beneficial effect of oestrogens on disease activity in postmenopausal female patients with rheumatoid arthritis.

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Epidemiological and immunological data suggest that female hormones may play a role in the aetiology and course of rheumatoid arthritis (RA). There is a clear female to male preponderance of the disease.¹ In women the use of oral contraceptives may protect against development of RA or reduce the severity of the disease.^{2,3} Disease symptoms are generally less in the second half of the menstrual cycle when sex steroid levels are high,⁴ whereas the risk of developing the disease is highest at the age of the menopause.⁵ During pregnancy there is often a decrease in disease activity of RA, with a flare up in the weeks after delivery.⁶ In animal models adjuvant oestrogens have been shown to suppress collagen induced arthritis.⁷ Most circumstantial data until now suggest a beneficial effect of oestrogens on disease activity.⁸

A few small uncontrolled studies have investigated possible therapeutic effects of sex hormones on human disease, with conflicting results.^{9–11} Recently two small studies, with a different design have been reported. One of them reported some, and the other no beneficial effect of oestrogens on disease activity in women with RA.^{12,13} To investigate

the possible beneficial effects of oestrogens on disease activity, we conducted a double-blind placebo-controlled study lasting one year in forty postmenopausal female patients with RA.

Patients and methods

Patients

Forty postmenopausal female patients with adult onset RA were admitted to the study; no contraindication for oestrogen treatment was found in any of the patients. Patients were considered to be postmenopausal when there had been no menstruation in the previous year. Patients using corticosteroids or hormonal replacement therapy were not allowed to participate in the study. All patients fulfilled the reviewed criteria for RA¹⁴ and had active disease defined by at least 3 of the following criteria: a) more than 6 painful joints; b) more than 3 swollen joints; c) erythrocyte sedimentation rate >28 mm/h; d) morning stiffness >45 minutes. When patients used disease modifying anti-rheumatic drugs (DMARD), these were used in a constant dose for at least three months before the start of the study and the dose of these drugs was kept stable during the study.

Study design

The trial was a double-blind controlled study comparing the additional effect of 2 mg oestradiolvalerate (Progynova[®]) and placebo for 52 weeks. Patients were randomly allocated to one of the two treatment groups. Oestradiolvalerate and placebo were provided in indistinguishable capsules. The capsules were taken in cycles of 84 days. The last 10 days of each cycle the patients received 200 mg progesterone (Progestan[®]) to induce a withdrawal bleeding. To try to maintain the double-blind character of the study and to control for a possible effect of progesterone the patients receiving placebo were also treated with progesterone. After each cycle of 84 days the trial medication was discontinued for 1 week. The complete trial consisted of 4 cycles.

Evaluation

Clinical and laboratory assessment of disease activity was performed every 2 months. For joint evaluation both the Ritchie articular index and the Thompson articular index were recorded.^{15–17} All joint scores were assessed by the same observer. Pain was recorded on a 100

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Table 1 Demographic and disease characteristics of 40 patients (start of the study)

Characteristic	Oestrogen group (n = 20)	Placebo group (n = 20)
Age in years (SD)	61 (5)	63 (8)
ARA functional class (SD)	I II III IV	3 15 2 0
Disease duration in years (SD)	9.1 (4.2)	9.0 (5.7)
Rheumafactor positive (%)	20 (100%)	17 (85%)
Erosions (%)	19 (96%)	20 (100%)
NSAID use (%)	17 (85%)	17 (85%)
DMARD use (%)	17 (85%)	17 (85%)
anti-malarials	1	2
sulphasalazine	9	8
gold (oral)	3	2
gold (intra-muscular)	2	1
methotrexate	2	4
none	3	3
Disease activity parameters*		
Ritchie score (SD) (range 0–76)	16.1 (4.8)	16.6 (6.4)
Thompson score (SD) (range 0–534)	170 (86)	171 (89)
Pain score VAS (SD) (range 0–100)	36 (13)	43 (12)
VDF/HAQ (SD) (range 20–80)	38 (13)	39 (11)
ESR (SD)	37 (15)	33 (15)

*a high score denotes more disease activity.

mm horizontal visual analogue scale (0 = no pain; 100 = worst pain possible). The following laboratory parameters were measured: erythrocyte sedimentation rate (ESR) and sex hormone binding globulin (SHBG). A standardised questionnaire on daily activities (VDF), a validated Dutch version of the HAQ¹⁸ was recorded at the start, after six months and twelve months (range of VDF/HAQ is 20–80; a low score denotes a good functional capacity).

Ethics

The approval of the Medical Ethics Committee of the University Hospital Utrecht was obtained. All patients gave their informed consent.

Statistics

After performing statistical tests for normal distribution (Number Crunches Statistical System), the following statistics were used in analysing the data: paired *t* tests (within the same treatment group) and two sample *t* tests (between treatment groups). *P* values <0.05 were considered statistically significant. For 2 variables, that is, the Ritchie and pain score, a power analysis was performed.¹⁹ The study power was increased by calculating a Pooled Index.²⁰ For this Pooled Index the following disease parameters were used: Thompson joint score, pain, VDF/HAQ and ESR. For these parameters the standardised variables were calculated: standard variable = (variable measured – mean)/standard deviation. For all standard variables the sign was adjusted so that positive values indicate improvement for the

patient and negative values indicate that the patient has deteriorated. The pooled index is the arithmetic mean of these 4 standardised variables.

Results

Patients studied

Forty postmenopausal patients with RA entered the study. Thirty four patients (85%) were taking non-steroidal anti-inflammatory drugs (NSAID) and thirty four patients (85%) used different DMARD. Characteristics of patient groups at the start of the study are shown in table 1. After disclosure of the coding the two groups proved to be comparable for all demographic characteristics and disease activity parameters.

Withdrawals

Seven of the 40 patients who entered the study withdrew before completing the full 52 weeks. After disclosure of the coding, 5 of the 7 patients were in the oestrogen group and 2 in the placebo group. During the first three months of the trial 3 patients withdrew because of irregular menstrual bleeding, all three patients were in the oestrogen group. The other 4 withdrawals, 2 in the oestrogen and 2 in the placebo group, discontinued between week 26 and 52 because of lack of efficacy. Patients who dropped out from the study were included in the results until withdrawal.

Side effects

Apart from withdrawal bleeding, no side effects were seen in the patients taking oestradiolvalerate. Most patients (70%) taking oestrogens had a withdrawal bleeding, while none of the patients taking placebo experienced a withdrawal bleeding.

Compliance

To check patients' compliance to the study SHBG levels were measured. In all women taking oestrogens SHBG increased considerably. In table 2 mean values are given.

Parameters of disease activity

The data of the Thompson articular index and ESR of both treatment groups are illustrated in the figure. No significant difference at any assessment during the trial was observed within the treatment regimes for both parameters. Results of changes in all disease activity measurements within each treatment group at the start, after 6 and 12 months are shown in table 3. No statistically significant change of any disease activity parameter was seen after six and twelve months within both treatment groups. Statistical analysis of changes in disease activity parameters between both treatment groups showed no statistically significant differences, except for worsening of the pain in the oestrogen group versus the placebo group (table 4).

Calculations showed that our sample size had a power of 80% in detecting a difference of 6.9 in Ritchie score and 13.7 mm in pain score between the two treatment groups. In

Table 2 Sex hormone binding globulin (SD) levels in both treatment groups during the study

Months	Oestrogen group	Placebo group	<i>p</i> value*
0	51 (14)	56 (21)	0.5
6	87 (34)†	55 (23)	0.003
12	84 (26)†	57 (20)	0.002

*2 sample *t* test.

†paired *t* tests (*p* < 0.005).

Figure A: The mean Thompson articular index (SD) of both groups during the study year. (Y-axis: Thompson articular index, X-axis: time in months); B: The mean ESR (SD) of both groups during the study year. (Y-axis: ESR, X-axis: time in months).

Table 3 Changes in disease activity variables from base-line values after 6 and 12 months. Differences within both treatment groups

	Oestrogen group						Placebo group					
	6 months (n = 17)			12 months (n = 15)			6 months (n = 20)			12 months (n = 18)		
	Mean	95(%) CI	p value	Mean	95(%) CI	p value	Mean	95(%) CI	p value	Mean	95(%) CI	p value
Ritchie score	0.1	-3.7 to 4.0	0.9	-0.3	-4.2 to 3.7	0.9	-0.8	-5.5 to 4.0	0.7	-1.3	-5.2 to 2.5	0.9
Thompson score	9	-60 to 77	0.8	17	-40 to 70	0.5	-25	-68 to 19	0.2	-3.3	-50 to 43	0.5
Pain score VAS	10	-3 to 22	0.1	9	-1 to 19	0.07	0	-1 to 1	1	-4	-11 to 4	0.3
VDF/HAQ	1	-3 to 5	0.5	1	-4 to 6	0.6	-4	-11 to 3	0.2	-1	-4 to 6	0.2
ESR	6	-2 to 14	0.1	7	-1 to 16	0.2	2	-11 to 6	0.6	4.5	-0.2 to 9.3	0.4

*paired t test.
CI = confidence interval.

Table 4 Changes in disease activity variables from base-line values after 6 and 12 months. Differences between the two treatment groups: oestrogen group n = 17 at 6 months, n = 15 at 12 months; placebo group n = 20 at 6 months, n = 18 at 12 months

	Oestrogen versus placebo group					
	6 months			12 months		
	Mean	95(%) CI	p value	Mean	95(%) CI	p value
Ritchie score	0.9	-5.3 to 7.1	0.76	1.5	-3.8 to 6.8	0.56
Thompson score	33	-42 to 108	0.37	21	-49 to 92	0.54
Pain score VAS	10	-6 to 26	0.20	14	3 to 25	0.01
VDF/HAQ	2	-3 to 7	0.45	3	-3 to 10	0.27
ESR	4	-8 to 15	0.54	5	-6 to 16	0.36

CI = confidence interval.

table 5 the Pooled Index, using Thompson joint score, pain, VDF/HAQ and ESR is given. No statistically significant changes were observed.

In addition all individual patients were evaluated. When a patient improved 30% or more on at least 3 disease parameters this patient was considered improved; if there was a deterioration of 30% or more in at least 3 disease parameters we considered this patient

to have deteriorated. After 12 months of oestrogen treatment 1 patient was improved, 2 had deteriorated and 12 had no clinically relevant change in disease activity. After 12 months of placebo the figures were: 2 improved, 2 deteriorated, 14 no change. Fisher exact test improved versus deteriorated plus no change, showed that there was no significant difference between both treatment groups.

Discussion

The influence of female sex hormones on RA has been the subject of investigations in different areas. Most data, both from epidemiological studies in women with RA and from animal models of adjuvant arthritis, suggest a beneficial effect of female sex hormones.²¹ In the 1960s a few open studies with Enovid^R, a progestagen with some oestrogenic properties were undertaken, with conflicting results; two studies reported a favourable effect and in one study no beneficial effect was found.⁹⁻¹¹ Recently, two different studies investigated the influence of oestrogens upon disease activity of RA. Bijlsma *et al* performed a pilot trial on the effect of 12.5 µg ethinyloestradiol in three premenopausal and seven postmenopausal female patients with RA, in a double-blind crossover study lasting 6 months. All other medication was kept stable during the study. Although the number of patients was small some beneficial effect was detected.¹² Hazes *et al* investigated the effect of Lyndiol^R, each tablet containing 2.5 mg lynestrenol and 50 µg ethinyloestradiol, on 10 premenopausal patients with moderate active RA in an open study during six months.¹³

Table 5 Changes in Pooled Index of disease activity variables from base-line values after 6 and 12 months (a negative value means a deterioration)

A Differences within both treatment groups	Oestrogens		Placebo	
	6 months	12 months	6 months	12 months
Pooled index	-0.26	-0.28 (all not significant)	0.05	0.10
B Differences between the two treatment groups				
	oestrogens v placebo			
	6 months	p	12 months	p
Pooled index	-0.31	0.23 (all not significant)	-0.38	0.07

Except for the number of swollen and tender joints, no other clinical or laboratory parameter improved. Until now no placebo-controlled studies have been reported on the possible therapeutic effect of oestrogens on disease activity in patients with RA. The technical difficulties of and the need for such an intervention study have been the subject for discussion amongst researchers.²¹ We chose to investigate the effects of oestrogens in postmenopausal patients with RA because the oestrogen levels in peripheral blood are low and if there was to be a beneficial effect from female sex hormones it would be more noticeable in postmenopausal women. In addition there is no menstrual cycle in postmenopausal women which might interfere with the study design or interpretation of the results.

The results of our placebo-controlled study show no beneficial effect of 2 mg oestradiolvalerate on disease activity parameters. In this study only 5 different disease parameters reflecting various important aspects of RA activity were assessed. The use of only a limited number of parameters for assessing disease activity in RA was recently advocated in an article concerning measurements of disease activity in trials.²² Also the method of the Pooled Index did not show any beneficial effect of oestradiolvalerate. If there was any trend at all, it showed a deterioration instead of an improvement of disease activity. How reliable and relevant are these negative results?

We do not think that the dose of 2 mg oestradiolvalerate, which is equivalent to 25 µg ethinyloestradiol, was too low; this dose is nearly twice as high as that used for perimenopausal complaints and has proved effective in the prevention of postmenopausal bone loss. The use of a higher dose of oestrogen in postmenopausal patients for a prolonged period of time would probably be unethical because of the chance of serious side effects. We do not think that the small dose progesterone given to both groups for 10 days during each 84 day cycle could have had any influence on disease activity.

All patients had sufficient disease activity at the start to detect a change of disease activity if there was really an effect. The study period of one year is long enough to detect beneficial changes in RA activity on this medication.

The wide range of the 95% confidence intervals in tables 3 and 4 are due to the rather small number of patients studied as well as to the heterogeneity of the patient groups. It is thus possible that a conclusion based only on analysis of the means could be biased by a type II error. However, additional analyses were performed, based on changes in individual patients and on a Pooled Index and these did not show any improvement of disease activity during oestrogen treatment. Undetected possible changes in disease activity are unlikely to be clinically relevant.

In conclusion, no clear beneficial effect of adjuvant therapy with oestradiolvalerate on disease activity in postmenopausal patients with RA was seen in this placebo-controlled double-blind study. Our results show that there is no place for the therapeutic use of adjuvant oestrogens to diminish disease activity of RA. This treatment, however, may improve bone mineral density in these patients.²³

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