Endometrial Effects of Long-Term Mifepristone (MIFE) Treatment of Cushing's Syndrome: Results from the SEISMIC studies

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Potential conflict of interest may exist. Refer to the abstract.

Poster Board # SUN-52

BACKGROUND

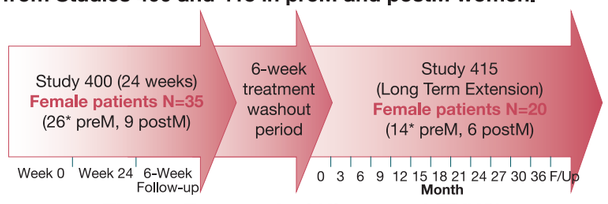
Progesterone receptor modulating drugs have been associated with changes in the histology of the endometrium known as progesterone-receptor modulator (PRM)-associated endometrial changes (PAEC).[1,2,3]

Mifepristone (MIFE) is a competitive progesterone receptor antagonist[4] and has been reported to cause PAEC at doses that are not associated with glucocortoid receptor (GR) receptor antagonism (5.0-200 mg daily),[1] therefore PAEC was anticipated during SEISMIC (**S**tudy of the **E**fficacy and **S**afety of **M**ifepristone in the Treatment of Endogenous **C**ushing's Syndrome) and the subsequent long-term extension study. Here we evaluate the endometrial effects of long-term treatment with MIFE.

STUDY DESIGN

- The SEISMIC Study (400) was a 24-week, open-label study of the administration of MIFE to subjects with Cushing's Syndrome (CS).
- The SEISMIC Extension Study (415) evaluated the long-term administration of MIFE to subjects with CS who completed the 24-week, open-label study and agreed to participate in the extension trial.
- Female patients ≥18 years old with endogenous CS and Type 2 diabetes (or impaired glucose function) AND/OR hypertension were followed from baseline at the start of SEISMIC through the long-term follow-up study, until patient withdrawal from the trial or until the drug was available commercially.
- Patients with endometrial thickness (ET) >20 mm for premenopausal (preM) patients and >5 mm for postmenopausal (postM) patients, ovarian cyst(s) (preM >5 cm / postM >2 cm) or, in Study 400, free fluid pockets >4 cm were excluded from the SEISMIC studies.
- These studies included transvaginal ultrasound (TVUS) and endometrial biopsies for female subjects with an intact uterus to evaluate ET.

Figure 1. Study design: Evaluation of the endometrial changes from Studies 400 and 415 in preM and postM women.



* 3 women did not undergo TVUS due to hysterectomy or endometrial ablation prior to study entry.

RESULTS

Table 1. Demographics of the patients evaluated for endometrial effects during the SEISMIC studies.

Demographic	Premenopausal	Postmenopausal
Patients N	26	9
Baseline TVUS N	18	8
Post-baseline TVUS N	19	8
Weight at entry to Study 400 - mean (median; min, max) kg	95.4 (89.9; 61.3, 158.2)	92.4 (83.5; 66.6, 138.6)
Age mean (median; min, max)	39 (39.0, 26, 51)	57.0 (57.0; 46.0, 66.0)

- 26 (18 preM / 8 postM) baseline and 27 (19 preM / 8 postM) post-baseline TVUS were performed during Studies 400 and 415 (Table 1).
- Median [range] ET for preM and postM pts was 5.0 [1.0-13.0] and 3.0 [2.0-8.0] mm at baseline vs 11.0 [4.8-55.0](P<0.01) and 6.4 [1.0-17.0] mm (P=0.25) at 6 mo (end of Study 400), respectively (Figure 2).
- ET increases of >5mm occurred in 8 preM and 1 postM; of those, 4 preM and 1 postM had an increase of greater than 10mm.
- During extended follow-up in 18 pts (median of 26.9 [13.7-43] mo) there were continued increases in ET (see Figure 2).
- Vaginal bleeding occurred in 10 preM and 2 postM patients.
  - o Minor bleeding occurred at initiation (3 preM) and termination (1 preM) of MIFE treatment in 4 preM.
  - o Intermittent self-limited spotting or bleeding occurred in 2 preM and 2 postM patients during treatment.
  - o Clinically relevant bleeding occurred at ≥ 14 weeks of treatment in 4 preM with ET > 20 mm (median 38 [25-55] mm). Three of these women underwent hysterectomy and one a D and C and all remained on MIFE throughout the trial.
  - o Increases in ET were not uniformly accompanied by bleeding. There was no bleeding in 3 patients with ET > 20mm beyond 6 month.
- Thirty-three endometrial biopsies were obtained in 11 preM and 4 postM patients.
  - o Of the 33 biopsies obtained, benign histology with variable patterns of inactive, atrophic, disordered or mixed pattern endometrium was observed in 94%; findings of PAEC (Figure 3) was seen in 56.2%.
  - o In one patient, simple hyperplasia could not be confirmed on a repeat biopsy.
  - o Complex atypical endometrial hyperplasia was noted in a second patient and was thought to have existed prior to study entry.
  - o No patient had evidence of endometrial carcinoma.

Figure 2. Endometrial thickness in preM and postM patients with baseline and at least one follow-up TVUS evaluating endometrial effects of treatment with MIFE during the SEISMIC studies.

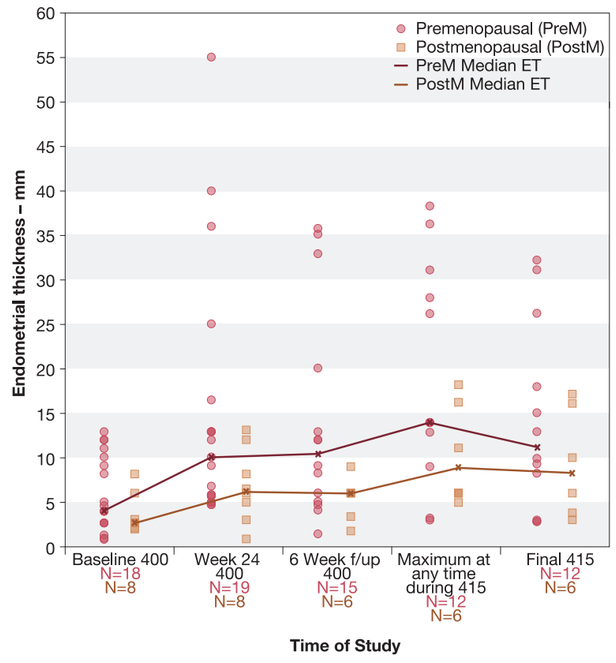
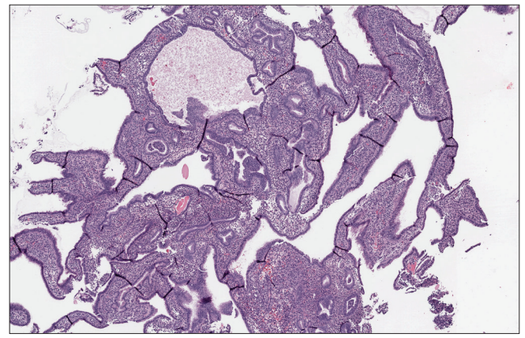


Figure 3. Endometrial biopsy showing characteristic morphologic features of PAEC: large thin-walled cysts with depleted intervening stroma. The glandular epithelium exhibits variable secretory changes with apoptotic figures and rare mitoses.



DISCUSSION/CONCLUSION

- Histological changes consistent with PAEC were observed in 56.2% of female CS patients who had biopsies in SEISMIC and the extension study who received chronic MIFE at doses of 300 - 1200 mg daily. These findings are similar to those reported when MIFE is used at low doses which do not produce glucocorticoid antagonism.[1]
- MIFE use was associated with endometrial thickening on TVUS and was more prominent in preM patients than postM.
  - o Clinically significant bleeding may occur during chronic MIFE therapy and is usually seen in preM women with ET > 20mm.
- Chronic use of MIFE (300-1200 mg) in women with CS was not associated with precancerous endometrial lesions.
- Gynecological consultation may be required in patients with persistent endometrial bleeding.

ACKNOWLEDGEMENTS

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