Medical treatment for uterine fibroids

Prof Mary Ann Lumsden
Prof of Gynaecology and Medical Education
University of Glasgow
Senior Vice President RCOG
Conflict of Interest

Chair, Guideline development Group for Guideline No 44, Heavy Menstrual Bleeding.

Topic Expert on NICE Standing Committee A
Addendum to Guideline No 44 (Selective Progesterone Receptor Modulators)
Control of Growth

- Oestrogen
  - Removal of oestrogen stimulation leads to fibroid shrinkage and relief of fibroid-associated symptoms
- Progesterone
  - Role less clear but appears to stimulate growth
Selection of patients with uterine fibroids

Figure 1  Changes in fibroid volume during treatment with goscrelin
4 = Severe
3 = Moderate
2 = Mild
1 = None

Patient outcomes:
- Dysmenorrhea
- Pelvic Pain
- Deep Dyspareunia
- Pelvic Tenderness
- Pelvic Induration

* LUP/N = LUPRON DEPOT 3.75 mg plus noradrenaline acetate 5 mg daily
Fig. 2. Total uterine volume (cm³) changes in 10 patients with uterine fibroids, during and after treatment with intranasal buserelin.
GnRH Agonists and ‘Add Back’

- HRT
  - Tibolone
  - Oestradiol 1mg + progestagen (or equivalent)
- Progestagen
- Oestradiol (low dose)
- Bisphosphonate
GnRH Antagonists

- 1\textsuperscript{st} generation associated with histamine release
- 2\textsuperscript{nd} generation well tolerated and active orally
- Cause suppression of gonadotrophins and oestradiol although initial effect dependent on stage of menstrual cycle at initiation of treatment.
- Hypoestrogenic side effects appear to be dose related.
- Useful for hormone dependent disease although full suppression does not occur.
- Most data is on use in endometriosis (Elagolix)
LNG-IUS
LNG-IUS

- Useful for
  - small fibroids (<5cm)
  - Intramural or sub-serosal
- Not suitable when cavity distorted
- No change in myoma volume
- May come out during menses
- Increases haemoglobin levels
- Useful in presence of ademomyosis
- Contraceptive
Anti-progestins

Fig. 1. Chemical structure of SPRMs.

N. Chabbert-Buton et al. / Molecular and Cellular Endocrinology 358 (2012) 232–243
Mechanism of Action

A

Agonist

PR

PR

COACTIVATORS

Transcription activation

B

Antagonist

PR

PR

COREPRESSORS

No activation of transcription

N. Chabbert-Buffet et al. / Molecular and Cellular Endocrinology 358 (2012) 232–243
Ulpiristal Acetate versus Placebo for Fibroid Treatment Before Surgery

Jacques Donnez, M.D., Ph.D., Tetyana F. Tatchuck, M.D., Ph.D., Philippe Bouchard, M.D., Lucian Puscasu, M.D., Ph.D., Nataliya F. Zakharenko, M.D., Ph.D., Tatiana Ivanova, M.D., Ph.D., Gyula Ugocsai, M.D., Ph.D., Michal Mara, M.D., Ph.D., Manju P. Jilla, M.B., B.S., M.D., Elke Pestel, M.D., Paul Terrill, Ph.D., Ian Osterloh, M.R.C.P., and Ernest Lournaye, M.D., Ph.D., for the PEARL 1 Study Group*
Ulipristal Acetate versus Leuprolide Acetate for Uterine Fibroids

Jacques Donnez, M.D., Ph.D., Janusz Tomaszewski, M.D., Ph.D.,
Francisco Vázquez, M.D., Ph.D., Philippe Bouchard, M.D.,
Boguslav Lemieszchuk, M.D., Francesco Baró, M.D., Ph.D., Kazem Nouri, M.D.,
Luigi Selvaggi, M.D., Krzysztof Sodowski, M.D., Elke Bestel, M.D.,
Paul Terrill, Ph.D., Ian Osterloh, M.R.C.P., and Ernest Loumaye, M.D., Ph.D.,
for the PEARL II Study Group*
Proportion of patients with at least one daily PBAC ≥ 10 from Day 11 to Day 28

<table>
<thead>
<tr>
<th></th>
<th>UPA 5 mg</th>
<th>UPA 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion</td>
<td>4/93 (4.3%)</td>
<td>1/95 (1.1%)</td>
</tr>
<tr>
<td>UPA 10 mg</td>
<td>37/93 (39.8%)</td>
<td></td>
</tr>
</tbody>
</table>

GnRHa, gonadotropin-releasing hormone agonist; PBAC, Pictorial Bleeding Assessment Chart; UPA, ulipristal acetate (ESMYA®)

**SUBMUCUS FIBROIDs AND BLEEDING PATTERNS IN PEARL I**

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=48</th>
<th>UPA 5 mg n=95</th>
<th>UPA 10 g n=94</th>
<th>UPA Group n=189</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Submucous Fibroid</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>4.0%</td>
<td>68.6%</td>
<td>72.5%</td>
<td>70.3%</td>
</tr>
<tr>
<td>NO</td>
<td>13.5%</td>
<td>31.6%</td>
<td>93.8%</td>
<td>95.6%</td>
</tr>
<tr>
<td><strong>Bleeding Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Bleeding + Infrequent Bleeding</td>
<td>4.0%</td>
<td>68.6%</td>
<td>72.5%</td>
<td>70.3%</td>
</tr>
<tr>
<td>Regular Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular Bleeding</td>
<td>84%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Other Bleeding Patterns</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged Bleeding</td>
<td>4.0%</td>
<td>5.9%</td>
<td>5.0%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Frequent Bleeding</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Irregular Bleeding</td>
<td>8.0%</td>
<td>7.8%</td>
<td>5.0%</td>
<td>6.6%</td>
</tr>
<tr>
<td>3 Patterns</td>
<td>4.5%</td>
<td>4.5%</td>
<td>27.5%</td>
<td>29.7%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Despite the presence of submucosal fibroids, the majority of patients after UPA 5 mg or UPA 10 mg treatment are in category of «No Bleeding»

In untreated placebo women the predominant bleeding pattern is regular heavy periods.

If a patient still have "Other bleeding patterns" (irregular, frequent or prolonged bleeding) after UPA treatment, it's likely to be a patient to have submucosal fibroids.
Women with sub-mucous fibroids are more likely to have 1 of the 3 “Other bleeding patterns” (irregular, frequent or prolonged) likely to impact on QoL than those without submucous fibroids.
PEARL 111

- Open label Phase 3 trial
- 209 women with symptomatic fibroids
- 4 x 3 month courses of UPA 10 mg alternating with norethisterone or placebo
- 132 women entered the ‘extension study’
- Reduction in bleeding greater in those receiving NETA than placebo (PBAC scores 55 and 13 respectively)
Donnez et al 2014
Outcomes

• Menstrual blood loss
• Size of dominant fibroid.
• Uterine size
• Endometrial thickness/hyperplasia.

(other outcomes e.g., fertility were considered and the reviews (where data available) are included in Addendum)
Addendum to Clinical Guideline 44, Heavy menstrual bleeding: assessment and management

Clinical Guideline Addendum 44.1
Methods, evidence and recommendations
August 2016

Developed by the National Institute for Health and Care Excellence
1.5 Ulipristal acetate 5mg vs Placebo

Figure 37: Menstrual blood loss (pictorial blood loss assessment, change from baseline), 0-3 months treatment

<table>
<thead>
<tr>
<th>Ulipristal acetate 5mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Median</td>
</tr>
<tr>
<td>123</td>
<td>-360</td>
</tr>
<tr>
<td>48</td>
<td>-20</td>
</tr>
</tbody>
</table>

Median difference relative to Placebo (Pictorial blood loss assessment score change from baseline)

2

Figure 38: Fibroid volume (% change from baseline), 0-3 months treatment

<table>
<thead>
<tr>
<th>Ulipristal acetate 5mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Median</td>
</tr>
<tr>
<td>123</td>
<td>-21.2</td>
</tr>
<tr>
<td>48</td>
<td>-3.2</td>
</tr>
</tbody>
</table>

Median difference relative to Placebo (% change from baseline)
Figure 48: Fibroid volume, (ratio relative to baseline), 0-3 months treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Geo Mean</th>
<th>0.56</th>
<th>0.38</th>
<th>0.54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupractal acetate 5mg</td>
<td>Donnez 2012b99</td>
<td>93</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 49: Uterine volume, (ratio relative to baseline), 0-3 months treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Geo Mean</th>
<th>0.34</th>
<th>0.22</th>
<th>0.30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupractal acetate 5mg</td>
<td>Donnez 2012b99</td>
<td>93</td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Offer ulipristal acetate 5mg (no more than 4 courses) to women with fibroids 3 cm or more in diameter and a haemoglobin level of 102 g/l or below.

• Consider ulipristal acetate 5mg (no more than 4 courses) to women with fibroids 3 cm or more in diameter and a haemoglobin level above 102 g/l.
Information for women regarding potential ‘adverse’ effects.

<table>
<thead>
<tr>
<th>Ulipristal acetate [new 2016]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: endometrial thickening, amenorrhoea</td>
</tr>
<tr>
<td>Common: vertigo, nausea, abdominal pain, hot flushes, headache, fatigue, ovarian cyst, breast pain and tenderness, pelvic pain, musculoskeletal pain, acne, weight increase</td>
</tr>
<tr>
<td>Less common: dizziness, dry mouth, constipation, anxiety, urinary incontinence, alopecia, dry skin, hyperhidrosis, back pain, uterine haemorrhage, metrorrhagia, genital discharge, oedema, asthenia, increased blood lipids</td>
</tr>
<tr>
<td>Rare: epistaxis, dyspepsia, flatulence, ruptured ovarian cyst, breast swelling</td>
</tr>
</tbody>
</table>
RESEARCH ARTICLE

Safety after extended repeated use of ulipristal acetate for uterine fibroids

Bart C. J. M. Fauser, Jacques Donnez, Philippe Bouchard, David H. Barlow, Francisco Vázquez, Pablo Arriagada, Sven O. Skouby, Santiago Palacios, Janusz Tomaszewski, Boguslaw Lemieszczuk, Alistair R. W. William

PLOS ONE | DOI:10.1371/journal.pone.0173523 March 7, 2017
• PEARL Extension study 2
  – Open label
  – Extended up to 8 courses
  – Drug free period of 2 bleeds
  – Moderate to severe symptoms
  – Fibroids 3-10 cm (uterus <16 week size)
  – 64/99 participated
• Clinical Efficacy (not reported)
  – 17% drop out (11)
    • Lack of efficacy
    • Surgery
    • Pregnancy
    • other
• Histology
• Biochemical assessments
• Endometrial thickness
  – 2 patients > 16mm
  – All benign histology
Table 2. Summary of endometrium biopsy consensus and endometrium biopsy non-physiological descriptions (PAEC) (Full analysis set, N = 64).

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>After course 4</th>
<th>After Course 8</th>
<th>3-month after course 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Biopsies</td>
<td>52</td>
<td>61</td>
<td>48</td>
<td>24</td>
</tr>
<tr>
<td>Adequate Biopsies (1*)</td>
<td>50 (96.2%)</td>
<td>56 (91.8%)</td>
<td>43 (89.6%)</td>
<td>22 (91.7%)</td>
</tr>
<tr>
<td>Benign (2**)</td>
<td>50 (100%)</td>
<td>56 (100%)</td>
<td>43 (100%)</td>
<td>22 (100%)</td>
</tr>
<tr>
<td>Hyperplasia (2**)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Malignant neoplasm (2**)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-physiological changes observed by two or three pathologists**</td>
<td>9 (18.0%)</td>
<td>12 (21.4%)</td>
<td>7 (16.3%)</td>
<td>2 (9.1%)</td>
</tr>
</tbody>
</table>

1 Endometrium biopsy performed and assessment adequate by at least one pathologist.
2 Of those who deem specimen adequate, at least two assessors have the same opinion; otherwise the most severe is used.
* Denominator of percentage is the number of subjects that have endometrium biopsy performed.
** Denominator of percentage is the number of subjects with an adequate specimen.
Conclusions

- SPRMs being increasingly used
- Currently use 4 cycles of treatment with 1 menses between (20 months) depending on the license in any particular country
- Very effective in decreasing heavy menstrual bleeding
- Less impact than GnRH on fibroid and uterine size.
- No evidence for impact on surgery.
Thank you