A Pearl for Uterine Fibroids

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Uterine fibroids are the most common benign uterine tumors in women of reproductive age. Although benign, fibroids can cause in infertility and lower abdominal pain. The treatment modality is primarily surgical.

Why was this study done?

Few studies have explored the utility of medical interventions in the management of uterine fibriods. A 2011 report by the Agency of Healthcare Research and Quality [1] concluded that the literature examining the effectiveness of treatment strategies was scanty. Gonadotropin-releasing hormone (GnRH) analogues, such as leuprolide acetate, have shown promise in the suppression of uterine fibroids and in minimizing bleeding prior to surgery. A few small and uncontrolled studies [2] involving a class of drugs called selective progesterone receptor modulators (SPRM) have shown some effectiveness in medical management of uterine fibroids by reduction in uterine and fibroid size as well as by induction of amenorrhea prior to planned surgery. The present study was conducted to determine whether daily oral ulipristal acetate (5 mg or 10 mg) was non-inferior to a monthly intramuscular injection of leuprolide acetate (3.75 mg) in controlling bleeding as well as in its side-effect profile prior to a planned surgery.

How was this study done?

This study, titled PGL4001 Efficacy Assessment in Reduction of Symptoms Due to Uterine Leiomyomata (PEARL II), was a randomized, non-inferiority, parallel-group, double-blind, double-dummy, active-comparator-controlled, phase 3 trial to assess the efficacy of ulipristal acetate and leuprolide acetate in symptomatic, preoperative management of uterine fibroids.

A comparator controlled trial is undertaken when there is considerable and established evidence of a treatment of a given condition that has better outcomes than placebo.

In such a situation, a test treatment (in this case, ulipristal acetate) is compared with the standard treatment (leuprolide acetate). Phase 3 of a clinical trial involves the final testing of the substance/treatment choice by randomization and blinding. In this study, a double-dummy design was incorporated which is a further enhancement to reduce bias. This design involves administering both the test and standard substance to a given participant at alternating periods during the study.

PBAC (pictorial blood-loss assessment chart) score ranging from 0 to 500 (higher numbers denoting increasing severity) was used as an objective method to assess the degree of uterine bleeding. Eligibility criteria for this study were a minimum PBAC score of 100, which defines menorrhagia (blood loss of more than 80 ml).

Efficacy end points (At week 13)

1. Primary - Proportion of patients with controlled uterine bleeding (PBAC score < 75)
2. Secondary
   - Bleeding pattern (consecutive 28-day PBAC scores)
   - Amenorrhea (28-day PBAC score ≤ 2)
   - Changes in uterine/fibroid size from baseline (on the basis of ultrasonography)
   - Global pain score (on the Short-Form McGill Questionnaire)
   - Uterine Fibroid Symptom and Quality of Life questionnaire
   - Hemoglobin levels

Safety end points (At week 13)

1. Primary
   - Serum estradiol levels
   - Proportion of patients reporting moderate to severe hot flashes during treatment
   - Serious adverse events (recorded up to week 38)
2. Secondary
   - Bone-turnover markers (bone-specific alkaline phosphatase, type 1 collagen C-telopeptide, type 1 procollagen, deoxypyridinoline)

- Levels of serum progesterone, estradiol, corticotrophin, thyrotropin and prolactin (recorded at baseline and at weeks 5, 9, 13 and 17)
- Endometrial thickness and assessment of ovaries (at weeks 13, 17, 26 and 38) by means of ultrasonography and endometrial biopsy

What did this study find?

Summarizing the results with respect to the primary end points: The differences between ulipristal acetate and leuprolide acetate were 1.2 percentage points (95% confidence interval [CI], −9.3 to 11.8) for the 5-mg group and 8.8 percentage points (95% CI, 0.4 to 18.3) for the 10-mg group. These results indicated non-inferiority for both doses of ulipristal in controlling bleeding (lower limit of the CI for both comparisons was more than the pre-specified non-inferiority margin of −20%). Subsequently, a post-hoc superiority analysis showed the superiority of the higher dose of ulipristal (10 mg) was superior to leuprolide for the control of bleeding (P=0.03).

And with respect to the secondary end points:

- Excessive bleeding was better controlled in patients receiving either 5 mg or 10 mg of ulipristal acetate than in those receiving leuprolide acetate (P<0.001 for both comparisons).
- Leuprolide and other GnRH agonists reduce the tumor bulk quickly during the course of therapy, but there is rapid regrowth following discontinuation of treatment. Ulipristal, on the other hand, shows signs that there may be more long term benefits with respect to reducing myoma size. Spontaneous regrowth of myoma was observed in leuprolide arm patients who did not undergo subsequent surgery in one month, while the regrowth was delayed in the ulipristal group by 6 months.

Ulipristal acetate in either 5 mg or 10 mg dose also fared better than leuprolide acetate with respect to the safety-related primary end points (P<0.001 for both comparisons), as shown below, although there were no significant differences among any of the three groups with respect to the secondary end points for adverse effects (other adverse effects and discontinuation).

What is the bottom line?

The study showed that 13-week therapy with ulipristal is non-inferior to leuprolide in the medical management of uterine fibroids prior to surgery. One of the concerns is the fact that the study was designed and supported by PregLem, the makers of ulipristal. Since surgery happens to be the curative and gold standard therapy for uterine fibroids, a study comparing the effect of ulipristal versus surgery would be a better indicator of the therapeutic benefits afforded by the drug. The limitation is that this trial does not compare the surgical and medical outcomes but only studies the efficacy of two choices for the medical management of leiomyoma.

The bottom line is that this study shows ulipristal to be safe but only marginally more effective than GnRH analogs in the treatment of uterine fibroids. However, more trials with increased duration of treatment as well as comparison to surgical outcomes would be desirable.

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