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Original Article

Real-world data of 197 patients treated with ulipristal acetate for uterine fibroids: PREMYA study French population main outcomes

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ABSTRACT

Objectives. – To characterize and describe treatment with ulipristal acetate (UPA) in a preoperative setting and to evaluate the safety, effectiveness, and Health Related Quality of Life (HRQoL) outcomes in a French population treated according to standard clinical practice.
Materials and methods. – Multicentre, prospective, non-interventional study (PREMYA) of patients diagnosed with moderate to severe symptoms of uterine fibroids and undergoing a preoperative treatment with UPA 5 mg (Esmya®). Patients were followed for a total of 15 months (3 months UPA treatment and 12 months after). Data were collected approximatively every 3 months according to centre usual visit schedule.
Results. – A total of 206 women were enrolled in France, of whom 197 were found to be eligible for data analysis. Physicians' assessments of patients' overall symptomatic changes, as measured on the Clinical Global Impression-Improvement (CGI-I) scale, indicated that 83.7% of patients were improved at end of treatment (month 3). On the patients' treatment benefit scale (PTBS), 94.7% of patients reported an improvement. These 2 measurements, pain and quality of life, remained improved after treatment cessation and during the entire period of follow-up. Only 58.4% of patients underwent surgery within the timeframe of the study follow-up of which the majority were of a conservative/minimal invasive nature.
Conclusion. – Many patients did not undergo surgery during the planned 12 months follow-up period after treatment whereas all patients had an indication of surgery. All measurements of treatment outcome were markedly improved by 3 months of UPA 5 mg treatment.
Clinical trial number. – NCT01635452.

Introduction

Uterine fibroids are benign, monoclonal, hormone-sensitive, smooth muscle tumors of the uterus. It has been reported that they are the most frequent solid pelvic tumors in women, affecting 20–40% of women during their reproductive years [1]. Most uterine fibroids are asymptomatic but, when symptomatic, they can result in heavy uterine bleeding, anemia, abdominal pressure, abdominal pain, increased urinary frequency, pregnancy complications and infertility, hence having a significant impact on quality of life [2–4]. In a French epidemiologic survey, women diagnosed with symptomatic uterine fibroids reported on average 2.8 symptoms during the last 3 months [5].

Uterine fibroids are a leading cause of hysterectomy in France [6]. Other procedures, which preserve uterus, may preserve fertility and are less invasive, include open or laparoscopic

Abbreviations: CGI-I, Clinical Global Impression-Improvement; PAEC, Progesterone receptor modulator associated endometrial changes; PTBS, Patients' Treatment Benefit Scale; UPA, Ulipristal acetate.

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myomectomy, uterine artery embolization and hysteroscopic resection of fibroids or endometrial ablation.

Among medical therapies available, gonadotrophin releasing hormone (GnRH) agonists were the first pharmacological treatments approved for the preoperative treatment of symptomatic uterine fibroids. GnRH agonists were also the first medical therapy to have clinical trial data demonstrating their effectiveness in correcting anemia when given concomitantly with iron therapy, reducing fibroid-related bleeding, and reducing fibroid and uterine volume [7]. However, GnRH agonists have several potential side effects, mainly menopausal symptoms including hot flushes, depression, mood swings, loss of libido, nervousness and vaginitis and their use is limited to 3 to 6 months as they can lead to loss of bone mineral density [8–10]. Other medical treatments currently prescribed in symptomatic uterine fibroids include oral contraceptives and progestins, but there is no clear evidence of their effectiveness in patients with heavy menstrual bleeding due to fibroids, and their impact on fibroid volume remains uncertain [11]. A Cochrane review performed in 2013 on progestins and progestin-releasing intrauterine system concluded that there is insufficient evidence to recommend their use in treating premenopausal women with symptomatic uterine fibroids [12].

Ulipristal acetate (UPA) is a selective progesterone receptor modulator (SPRM) demonstrating a predominant anti-progesterone activity [13]. It has been developed first as a preoperative treatment of moderate to severe symptoms of uterine fibroids. In this indication, clinical trials have shown that UPA significantly reduces uterine bleeding and myoma volume also resulting in clinically significant increases in hemoglobin and hematocrit levels and reductions in self-reported pain and discomfort due to fibroids [14,15]. After treatment cessation, the reduction of fibroids volume was sustained for up to 6 months for patients treated with UPA, due to documented apoptotic action [16], whereas with GnRH agonists, uterine fibroids started to grow again one month after the end of treatment [15].

Like other SPRMs, UPA can lead to a pattern of benign, non-physiological, endometrial histological features termed progesterone receptor modulator associated endometrial changes (PAEC) [17]. Follow-up of patients treated with 3 months of UPA showed that, six months after treatment cessation, the endometrium had returned to normal histology in the majority of patients (with only one case of polyp reported and no case of hyperplasia) [12–14].

PREMYA is an observational study conducted according to usual practice designed to provide real-world data on UPA effectiveness and treatment patterns in its first therapeutic indication: a single 3-month treatment period in patients having an initial surgical indication.

Considering the differences in patients' characteristics and management between different countries, the aim of this sub-analysis of the PREMYA study is to report the results for the patients included at French centres.

Materials and methods

Study design

This multicentre prospective, non-interventional study of patients diagnosed with moderate to severe symptoms of uterine fibroids and undergoing a preoperative treatment with UPA 5 mg (Esmya®) was performed at 73 clinical practice centres within the EU. Ten (10) French centres were involved in this study and actively enrolled patients.

The study was designed by the sponsor (PregLem SA) in accordance with European Medical Agency (EMA) requirements as part of the risk management plan. Enrolment was conducted between 24th May 2012 and 16th April 2014 for the total study population. In France, 1st patient was enrolled on 9th August 2013 (shortly after ESMYA® commercialisation on 2nd August 2013).

The study was approved by an Independent Ethics Committee, in each country or centre according to applicable local regulations, and was conducted in accordance with the International Conference on Harmonization-Good Clinical Practice guidelines. The data were collected and analysed by Quintiles, Route de Pallatex 29, 1162 St-Prex, Switzerland.

Study population

The target study population included premenopausal women who had a diagnosis of symptomatic uterine fibroids, an indication of surgery whatever the types of procedures and initiated preoperative treatment with UPA 5 mg. Consecutive patients who met the enrolment criteria were invited to participate in the study; once they agreed to attend all scheduled follow-up visits and complete all questionnaires and to sign and date an informed consent form, they were enrolled into the study.

Interventions and visits schedule

At the time of study start, UPA 5 mg was indicated for preoperative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age and, according to the approved label, should have been given as a 5 mg tablet once daily for a total treatment duration not exceeding 3 months. At the enrolment visit, the investigator (or designee) reviewed the study with the patient. Once informed consent had been obtained, the following data were collected: patient demographic characteristics, patient contact information, medical history of uterine fibroids (including date and method of diagnosis, current symptoms, past and current treatments, and modalities of UPA treatment), other medical and gynaecological conditions and concomitant medications.

At months 3, 6, 9, 12 and 15 from enrolment (or according to usual clinical practice at each centre), the following data (since the previous visit) were recorded: any changes in UPA dosing, discontinuation/interruption date of UPA, symptoms of uterine fibroids, diagnostic tests, surgical procedures for uterine fibroids, changes in concomitant medications, occurrence of serious adverse events (SAEs) and adverse events (AEs) either related to UPA treatment or leading to treatment discontinuation.

At the 3, 6, 9, 12 and 15 month visits, the investigator assessed how much the patient's symptoms related to fibroids had improved or worsened relative to the baseline state at UPA treatment initiation using the Clinical Global Impression-Improvement Scale (CGI-I). The CGI-I is a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

In addition, patients' perceptions of improvement in uterine bleeding were measured on the Patient Treatment Benefit Scale (PTBS). This is a 4-point scale designed to document patient perception of their condition. Patients were asked about their current situation compared to their situation prior to treatment with UPA. The response options were:

- 1: greatly improved;
- 2: somewhat improved;
- 3: no different;
- 4: worse.

This patient self-administered scale was administered at all visits except baseline.

The patient was also asked to rate the severity of her pain associated with uterine fibroids using a 10 cm Visual Analogue Scale (VAS). This patient self-administered assessment was completed at enrolment and at all follow-up visits.

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