European Journal of Obstetrics & Gynecology and Reproductive Biology 208 (2017) 91–96

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Expert Opinion

Real world data of 1473 patients treated with ulipristal acetate for uterine fibroids: Premya study results☆,☆☆

Hervé Fernandez[a,b,c,*], Torsten Schmidt[d], Martin Powell[e], Ana Patrícia Freitas Costa[f], Pablo Arriagada[g], Christian Thaler[h]

[a] Service de Gynécologie Obstétrique, Hôpital Bicêtre, GHU Sud, AP-HP, F-94276, Le Kremlin Bicêtre, France
[b] Inserm, Centre of Research in Epidemiology and Population Health (CESP), U1018, F-94276, Le Kremlin Bicêtre, France
[c] Faculty of Medicine, Univ Paris Sud, F-94276, Le Kremlin Bicêtre, France
[d] PAN-Klinik, Zentrum für gynäkologische Endoskopie, Zeppelinstraße 1, 50667 Köln, Germany
[e] CircleNottingham, Nottingham NHS Treatment Centre, Queen's Medical Centre Campus, Lister Road, Nottingham, NG7 2FT, United Kingdom
[f] Hospital do Espírito Santo – Évora, EPE, Gynaecology and Obstetrics Department, Largo Senhor da Pobreza, 7000-811, Évora, Portugal
[g] Gedeon Richter/Preglem S.A., Route de Frontenex 41A, 1207 Geneva, Switzerland
[h] Department of Obstetrics and Gynecology, Ludwig Maximilians Universität, Marchioninistr. 15, D-81377 Munich, Germany

ARTICLE INFO

Article history:
Received 30 June 2016
Received in revised form 24 October 2016
Accepted 10 November 2016

Keywords:
Bleeding
Pain
Quality of life
Ulipristal acetate
Uterine fibroids

ABSTRACT

Objectives: To characterize and describe treatment with Ulipristal acetate (UPA) in a pre-operative setting and to evaluate the safety, effectiveness, and Health Related Quality of Life (HRQoL) outcomes in a population treated according to standard clinical practice in the EU.
Study design: Multi-centre, prospective, non-interventional study (PREMYA) of patients diagnosed with moderate to severe symptoms of uterine fibroids and undergoing a pre-operative treatment with UPA (Esmya®) at 73 clinical practice sites within the EU. Patients were followed during UPA treatment and for 12 months after treatment discontinuation for a total of 15 months follow-up. Data was collected every 3 months in accordance with standard care visits.
Results: A total of 1568 women were enrolled, of whom 1473 were found to be eligible for data analysis. Only 38.8% of patients underwent surgery, of which the majority were of a conservative/minimally invasive nature. Physicians' assessments of patients' overall symptomatic change, as measured on the Clinical Global Impression-Improvement (CGI-I) scale, indicated that 60% of patients were much improved or very much improved at 3 months. Pain and quality of life after treatment cessation remain lower than baseline during the entire period of follow-up
Conclusions: The majority of patients do not undergo surgery immediately after treatment cessation. Quality of life and pain are highly improved by Esmya® treatment.

Introduction

Uterine fibroids are benign, monoclonal, hormone-sensitive, smooth muscle tumours of the uterus. They are the most common tumour of the female reproductive tract in pre-menopausal women, and have been reported to affect 20–40% of women during their reproductive years [1]. Although often asymptomatic, uterine fibroids can result in heavy uterine bleeding, anemia, abdominal pressure, abdominal pain, increased urinary frequency, pregnancy complications and infertility. Beyond their physical morbidity, uterine fibroids are a frequent cause of significant impairment of quality of life [2,3].

The current mainstay treatment for symptomatic uterine fibroids is surgery. Uterine fibroids are a leading cause of hysterectomy, which is the most commonly performed surgical treatment for this condition [4,5]. Other less invasive procedures include open or laparoscopic myomectomy, uterine artery embolization, and, if the dominant symptom is bleeding, hysteroscopic resection of fibroids or endometrial ablation.

In addition to ulipristal acetate 5 mg, the only other pharmaceutical treatments currently approved for the pre-operative

☆ Clinical trial number: NCT01635452.
☆☆ Commercial product mentioned in title: Ulipristal Acetate, Gedeon Richter Plc., Gyömrői út 19-21, H-1103 Budapest, Hungary.
* Corresponding author at: Hôpital Bicêtre - APHP, Service de Gynécologie-Obstétrique, 78 avenue, du Général Leclerc, Le Kremlin Bicêtre cedex, France.
E-mail address: herve.fernandez@aphp.fr (H. Fernandez).

http://dx.doi.org/10.1016/j.ejogrb.2016.11.003
0301-2115/

treatment of symptomatic uterine fibroids are gonadotropin releasing hormone (GnRH) agonists. These therapies are effective in reducing fibroid-related bleeding, correcting anemia when given concomitantly with iron therapy, reducing abdominal symptoms, and reducing fibroid and uterine volume [6,7]. However, the use of GnRH agonists in treating uterine fibroids is limited since suppression of estrogen to castration levels results in menopausal symptoms including hot flushes, depression, mood swings, loss of libido, nervousness and vaginitis [8]. Their use is restricted for up to a maximum of 6 months as they can lead to loss of bone mineral density. In addition, due to a flare effect, symptoms may initially worsen. Other medical treatments known to be used include oral contraceptives and progestins, but there is no clear evidence of their effectiveness in patients with heavy menstrual bleeding due to fibroids, and they have no effect on fibroid size [9].

Selective progesterone receptor modulators (SPRMs) offer a unique potential clinical application in gynaecology [10]. SPRMs demonstrate a predominant anti-progesterone activity and their administration can lead to a pattern of benign, non-physiological, endometrial histological features termed Progesterone receptor modulator Associated Endometrial Changes (PAEC). These changes are considered benign, and spontaneously reverse over a few weeks to several months following treatment discontinuation [10].

Ulipristal acetate (UPA) is an SPRM which effectively controls excessive bleeding due to uterine fibroids and leads to rapid fibroid shrinkage [11,12]. After treatment cessation, this reduction in fibroid volume can be sustained for up to 6 months, with menstruation usually returning within 4 to 5 weeks. In addition, treatment with UPA corrects haemoglobin and haematocrit levels, reduces fibroid-associated pain and improves quality of life [11,12].

At the time of study set-up, UPA 5 mg once daily was licensed for a 3-month pre-surgical treatment of fibroids. Since then, UPA is now indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

Although not a randomised clinical trial, the PREMYA study provides important and extensive real-world data relating to treatment patterns and clinical outcomes of UPA 5 mg taken once daily for 3 months in accordance with its first approved label for the pre-operative treatment of patients with uterine fibroids and moderate or severe symptoms.

Materials and methods

Study design

This multi-centre prospective, non-interventional study of patients, diagnosed with moderate to severe symptoms of uterine fibroids and undergoing a pre-operative treatment with UPA (Esmya®), was performed at 73 clinical practice sites within the EU.

The study was designed by the sponsor (PregLem SA). Enrolment was conducted between 24th May 2012 and 16th April 2014 in Germany, France, UK, Romania, Portugal, Sweden, Poland, Hungary, Slovenia and Austria. The study was approved by each centre's Independent Ethics Committee 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. This paper was prepared by the (first author) who vouches for the accuracy of the data.

Study population

The target study population included premenopausal women who had a diagnosis of symptomatic uterine fibroids, an indication of surgery with all types of procedure and initiated pre-operative treatment with UPA. Consecutive patients who met the enrollment 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.

Intervention and visit schedule

At the time of study start, UPA (Esmya®) was indicated for pre-operative 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 no longer than 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 was collected: patient demographic characteristics, patient contact information, history of uterine fibroids (including date and method of diagnosis, current symptoms, past and current treatments, and details of UPA treatment), other medical and gynaecological conditions and concomitant medications.

At Months 3, 6, 9, 12 and 15 from enrolment or according to the regular clinical practice at each site, the following data (since the previous visit) was 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, the occurrence of SAEs and adverse events (AEs) either related to UPA treatment or leading to discontinuation.

At the 3, 6, 9, 12 and 15 month visits, the investigator assessed how much the patient's symptomatic uterine fibroids had improved or worsened relative to the baseline state at the initiation of UPA treatment 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 compared to 3 months previous. The response options were: 1 = Greatly improved, 2 = Somewhat improved, 3 = No different, and 4 = Worse. This is a patient self-administered scale and 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. This is a patient self-administered assessment and was completed at enrolment and at all follow-up visits.

UFS-QOL Symptom severity scale has 8 items and contains questions on bleeding and bulk symptoms with a 3-month recall period. This assessment provides a tracking of patient symptoms. The inclusion of the symptom severity scale was used to evaluate continued symptom relief from treatment. This was a patient self-administered scale and was administered at enrolment and at all follow-up visits where available.

In terms of safety, during the course of the study, all related and non-related Serious Adverse Events (SAEs), all non-serious but related Adverse Drug Reactions (ADRs), all non-serious Adverse Events leading to Esmya® treatment discontinuation and all pregnancies occurring from the date of the signed informed consent were collected.

In this study, whenever any diagnosis of endometrial hyperplasia (simple, complex or atypical) or adenocarcinoma was made, whether resulting from endometrium biopsy or pathology examination of the uterus after hysterectomy, the investigator was asked to obtain pathology slides. The slides were sent for review by an independent pathologist if deemed appropriate by the investigator.