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Review

Ulipristal acetate for the management of large uterine fibroids associated with heavy bleeding: a review

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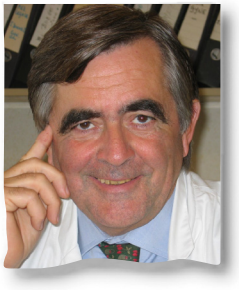

Jacques Donnez is since 2012 Professor Emeritus at the Catholic University of Louvain. He published over 600 original articles in peer-review journals.

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KEY MESSAGE

Ulipristal acetate, a selective progesterone receptor modulator, significantly reduces fibroid size and controls bleeding. It also significantly improves quality of life.

A B S T R A C T

Ulipristal acetate (UPA), a selective progesterone receptor modulator (SPRM), offers new therapeutic options for the clinical management of large uterine fibroids associated with heavy menstrual bleeding or with other moderate or severe symptoms (bulk symptoms, pelvic pain, decreased quality of life). SPRM are synthetic compounds that exert an agonist or antagonist effect on target tissues by their binding to progesterone receptors. UPA reduces fibroid size, controls bleeding in a high percentage of women and significantly improves quality of life. The present review aims to provide insights into UPA indications and its mechanism of action.

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Introduction

Ulipristal acetate (UPA) has a licence for use as a form of emergency contraception. Over the last 6 years, this has been extended to also cover uterine fibroids (Donnez and Dolmans, 2016; Donnez et al., 2012a, 2012b; Lumsden et al., 2015; Stewart, 2015) in women with uterine fibroids associated with heavy menstrual bleeding, or with other moderate or severe symptoms (bulk symptoms, pelvic pain, decreased quality of life [QOL]).

Oral contraceptives, progestins and levonorgestrel-releasing intrauterine systems (LNG-IUS) may be used 'off label' to treat women with gynaecological bleeding disorders, but they are not indicated for management of uterine fibroids, because fibroids are progesterone-sensitive (Chabbert-Buffet et al., 2005, 2014; Kim and Sefton, 2012; Wise and Laughlin-Tommaso, 2016) (**Table 1**). Oral progestogens are reported to reduce the symptoms or prevalence by 25–50% when administered during the second half of the cycle or as a 21-day contraceptive, but there are no data on continuous administration (Sayed et al., 2011; Venkatachalam et al., 2004). The LNG-IUS device is effective at reducing menstrual blood loss and restoring haemoglobin levels and may be an alternative to surgical treatment (Sayed et al., 2011), but its effect on the size of uterine myomas is still unclear (Murat Naki et al., 2010). Studies suggest that it could be a potentially good option for symptomatic women with no endometrial distortion (Sayed et al., 2011). Combined oral contraceptives have demonstrated improvements in menstrual blood loss, but no significant change in the volume of tumours (Sayed et al., 2011). For women with menorrhagia associated with small myomas (<3 cm) causing no distortion to the uterine cavity, the National Institute for Health and Care Excellence (NICE) guidelines (NICE, Clinical Guidance [Cg44] Last updated: August 2016) recommend that the following treatments may be considered: LNG-IUS, tranexamic acid, non-steroidal anti-inflammatory drugs, combined oral contraceptives or cyclic progestogens. For larger myomas or those distorting the uterine cavity and linked to menorrhagia, dysmenorrhoea or pressure symptoms, gonadotrophin-releasing hormone agonist (GnRHa) has been used to reduce myoma size and restore haemoglobin levels in symptomatic women (Donnez et al., 1989).

Table 1 – Contraindications and drug interactions.

General contraindications	Avoid UPA in patients with hypersensitivity to the substance or any of its excipients during pregnancy, breastfeeding, genital bleeding of unknown cause or for reasons other than uterine fibroids, and also in the presence of uterine, cervical, ovarian or breast cancer.
Specific contraindications	Use of UPA in women with severe asthma requiring oral glucocorticoids is not advised, as it exhibits some potential antagonist effects on glucocorticoid receptors. Use with kidney or liver disease Renal impairment is not expected to alter elimination of UPA. It is not recommended in patients with moderate and severe hepatic impairment. At the time of this manuscript, there is a review ongoing on liver parameters under UPA.
Drug interactions	SPRM are metabolized by the cytochrome P450 isoenzyme system and so drug–drug interactions may occur. Avoid co-administration of moderate (e.g. erythromycin, grapefruit juice, verapamil) or potent (e.g. ketoconazole, ritonavir, nefazodone, itraconazole, telithromycin, clarithromycin) CYP3A4 inhibitors and UPA. Concomitant use of UPA and CYP3A4 inducers (e.g. rifampicin, rifabutin, carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone) is not advised. Both CYP3A4 inhibitors and inducers may impact plasma levels of UPA, but the clinical effects of a lower or higher dose are unlikely to provoke any clinically significant response.

SPRM = selective progesterone receptor modulator; UPA = ulipristal acetate.

What is UPA?

UPA belongs to a class of drugs called selective progesterone receptor modulators (SPRM) (Chabbert-Buffet et al., 2005). They have a direct impact on fibroids, decreasing their size, and on the endometrium, reducing excessive bleeding. They are thought to modulate progesterone pathways known to play a key role in the development of uterine fibroids (Bestel and Donnez, 2014; Bouchard, 2014; Kim and Sefton, 2012; Moravek et al., 2015; Nieman et al., 2011; Nisolle et al., 1999; Spitz, 2009). There are four members of the SPRM family of compounds: mifepristone, asoprisnil, UPA and telapristone acetate.

Molecular mechanism of action of SPRM

SPRM are synthetic compounds that exert either an agonistic or antagonistic effect on target tissues determined by their binding to progesterone receptors (Bestel and Donnez, 2014; Chabbert-Buffet et al., 2005, 2014; Kim and Sefton, 2012), their action contingent on tissue type (Bouchard and Chabbert-Buffet, 2016; Donnez et al., 2015a; Moravek et al., 2015). Their mixed activity depends on recruitment of cofactors that regulate transcription in a so-called genomic pathway, as well as non-genomic interactions with other signalling pathways (**Figure 1**). Despite a number of recent hypotheses (Whitaker et al., 2017), it is not known exactly how SPRM alleviate menstrual bleeding (Williams et al., 2012).

Mechanisms of action in the response of uterine fibroids to UPA

UPA reduces fibroid size by a combination of proliferation inhibition, transitory stimulation of apoptosis and extracellular matrix (ECM) remodelling linked to high matrix metalloproteinase-2 (MMP-2) expression levels, particularly after long-term treatment (Courtoy et al., 2015). During the early phase of treatment, apoptosis is facilitated by temporary repression of survivin, an apoptosis inhibitor (Courtoy et al., accepted) (**Figure 2**). The reduction in fibroid volume is also correlated with high MMP levels and, conversely, low tissue inhibitor of metalloproteinase (TIMP) levels, suggesting that the MMP/TIMP balance plays an important role in ECM resorption in decreasing fibroid volume (Courtoy et al., 2018). Sustained fibroid shrinkage observed even after treatment cessation might therefore be the result of permanent ECM reduction. In the context of uterine fibroids, UPA does not alter expression patterns of progesterone receptors, nor their cofactors (Courtoy et al., 2017), indicating that the molecular mechanisms involved could be more complex than presumed.

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