NARRATIVE REVIEW

Expert opinion on the use of GnRH antagonists ± ABT in the treatment of symptomatic uterine fibroids: real-life experience of Italian centres

GnRH antagonists ± ABT in UF: Italian real-life experience

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ABSTRACT

Symptomatic uterine fibroids (UFs) are among the most common benign gynaecological conditions, significantly impacting women's quality of life. Current guidelines favour a stepwise management strategy beginning with appropriately tailored medical therapy. More than five years after their introduction in Europe, oral GnRH antagonists with or without add-back therapy (ABT) have accumulated substantial real-world clinical experience, enabling to identify their use in different clinical situations.

In the short/medium term, GnRH antagonists ± ABT effectively control moderate-to-severe UF symptoms and can be used in synergy with surgery, while overcoming the flare-up effect and route-of-administration limitations associated with GnRH agonists.

In the long term, these combinations represent optimal solutions for various patient categories, maintaining a stable estrogenic threshold within the so-called therapeutic window. This approach controls estrogen-dependent conditions – including concomitant adenomyosis or endometriosis – while preserving bone health through adequate ABT, thus balancing efficacy and safety. Importantly, this treatment also improves women's overall quality of life. In conclusion, GnRH antagonists ± ABT represent a versatile, personalized therapeutic option for women with symptomatic UFs across short, medium, and long-term clinical needs, supported by a well-established safety profile and a growing body of clinical evidence.

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INTRODUCTION

Symptomatic uterine fibroids (UFs) are among the most common benign gynaecological conditions [1, 2] and their transformation is exceedingly rare [3]. When UFs become symptomatic because of their number, size, or location, active treatment is advocated. Current recommendations favour a stepwise strategy, starting with appropriately tailored medical therapy and, when needed, proceeding to targeted fibroid removal to control symptoms while preserving uterine function where possible [4-7].

Five years have passed since the introduction, in Europe, of a new therapeutic category for the treatment of symptomatic UFs, namely GnRH antagonists with or without pre-combined add back therapy (ABT), administered orally [8].

Currently in Italy, there are two different oral formulations of GnRH antagonists available for the treatment of symptomatic UF:

- Relugolix 40 mg in fixed combination with add back therapy (1 mg of E2 + 0.5 of NETA) [9];

- Linzagolix in 100 mg and 200 mg dosages without fixed combination of add back therapy, but to be added where necessary and mandatory when using the 200 mg dosage for more than 6 months [10].

The rationale for their use relies on the blockade of the hypothalamic-pituitary-ovarian axis by the GnRH antagonist, which depending on the dosage can be total (relugolix 40 mg and linzagolix 200 mg) or partial (linzagolix 100 mg), with a peripheral reduction in the endogenous production of estrogens and progesterone by the ovary, resulting in the cessation of hormonal stimulation on the fibromatous neoformations [11]. The advantage compared to agonists is represented by the oral route of administration, the absence of flare-up, the rapidity of the onset of drug efficacy (hours for antagonists, days for agonists) and rapid cessation of the effect upon treatment discontinuation [12]. On the other hand, a potential limitation of GnRH antagonists lies in the intensity of central suppression they induce and the consequent degree of hypoestrogenism. This effect needs to be carefully titrated and monitored in accordance with the “estrogen threshold” theory [13, 14]. It is necessary, in fact, in women of childbearing age, to maintain an estrogen level at least equal to that of their early follicular phase (30-50 pg/ml) to avoid the damage that prolonged hypoestrogenism can cause, especially to allow maintenance of a proper bone metabolism balance and avoid loss of bone mineralization, which exposes to serious risk of fractures.

In Italy, the role of medical therapy as first-line treatment for symptomatic myomas has been well established for years [15]; in particular, there has been a shift from a lesion-oriented vision to a patient-oriented vision [12, 16].

Drawing on the growing body of literature on this topic – in particular, publications focused on the clinical use of GnRH antagonists with or without ABT (± ABT) in Europe following their approval for the management of symptomatic UFs, and supported by their extensive personal clinical experience – the authors aim to describe the patient settings and clinical situations in which these drugs demonstrate a genuine advantage, as well as their possible future fields of application.

The objective of this expert opinion is to share with Italian gynaecologists the clinical experience gained over recent years, in order to outline some optimal strategies for the use of GnRH antagonists ± ABT in the treatment of moderate-to-severe symptoms of UFs.

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CLINICAL UTILIZATION OF GNRH ANTAGONISTS (± ABT) IN THE SHORT TERM (APPROXIMATELY 3 MONTHS)

Early experiences focused on shorter-term use, building upon the already established practice of using GnRH agonists as bridging medical therapy in preparation for subsequent surgical intervention.

The advantages of short-term use are diverse and multifaceted. Patients with UFs scheduled for surgery frequently present with iron-deficiency anaemia resulting from heavy menometrorrhagia, which is one of the hallmark symptoms of fibroids with predominant submucosal involvement. Cycles of GnRH antagonists ± ABT, given their rapid action in resolving menometrorrhagic phenomena by inducing amenorrhoea in patients [17, 18], can improve the preoperative clinical status of patients, thus facilitate postoperative recovery and reduce morbidity [19]. It is important to note that preoperative anaemia is an independent risk factor for increased 30-day mortality (odds ratio 2.40, 95%CI 1.06-5.44) and morbidity (odds ratio 1.80, 95%CI 1.45-2.24) in gynaecological surgery [20, 21], as well as intraoperative and postoperative complications in fibroid removal procedures (odds ratio 5.3, 95%CI 4.3-6.4) [22].

Results from the registration RCTs of the two GnRH antagonists ± ABT demonstrate that after only 3 cycles, initially anaemic patients show an increase of at least 1 g/dL in haemoglobin levels [23], with a significant increase exceeding 2 g/dL after 6 treatment cycles [18].

According to a survey conducted by a national consumer association on surgical waiting lists in Italy, just over half of patients were admitted within the expected timeframe, with marked variability between regions [24]. Thus, treatment with GnRH antagonists ± ABT for even just a few months before surgery can be proved advantageous in managing moderate to severe symptoms in patients with UFs, in some cases allowing the conversion of a deferrable procedure (*i.e.*, non-urgent but not indefinitely postponable) into one that can be safely scheduled. Based on the authors' experience, preoperative treatment of UFs with GnRH antagonists in fixed combination with ABT [19], after only three months of use, significantly ($p < 0.001$) increased mean haemoglobin levels in the observed patients from 9.3 ± 1.1 to 11.6 ± 1.7 g/dL, representing a 25% increase. In 19 of 31 women (61.3%),

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haemoglobin levels increased by ≥2 g/dL. Moreover, in 26% of patients, the improvement in haemoglobin levels together with the reduction in myoma volume and related symptoms prompted a shared decision between surgeon and patient to temporarily defer surgery and extend medical therapy for a further three months before reassessment. Finally, preoperative therapy enabled the use of a less invasive surgical approach than previously planned, with intraoperative complications occurring in only 13% of cases [19].

In cases of very large uterine fibroids, when it is necessary to reach a significant volume reduction, the use of GnRH antagonists alone at highest dosage (*i.e*. 200 mg) allows a significant volumetric reduction and resolution of heavy menstrual bleeding [25].

CLINICAL UTILIZATION OF GNRH ANTAGONISTS (± ABT) IN THE MID-TERM (APPROXIMATELY UP TO 6 MONTHS)

Nowadays, conservative non-extirpative interventions for UFs are also available, including minimally invasive procedures such as ablative techniques (radiofrequency and/or microwave ablation, laser vaporization) and uterine artery embolization (UAE) [7, 26, 27]. These minimally invasive radiological techniques can benefit from a synergy with GnRH antagonists ± ABT for an intermediate period (approximately 6 months).

Experiences regarding the synergistic use of GnRH antagonists ± ABT with these techniques are currently sporadic; nevertheless, we consider it worthwhile to report a case of an 80 mm uterine fibroid causing bleeding and anaemia, for which, based on clinical history and previous surgical interventions, a conservative approach was adopted. This consisted of UAE with reduction of fibroid volume, followed by therapy with relugolix in fixed combination, which improved symptomatology and further contributed to reducing the size and vascularization of the fibroid itself, and finally, after six months, allowed mini-resectoscopic myomectomy under local anaesthesia [28]. These encouraging personal experiences will need to be confirmed by larger prospective studies.

A particularly sensitive topic concerns the possible interference of UFs with fertility issues, for example due to distortion of the uterine cavity, myometrial/endometrial vascular compromise, so-called increased “peristalsis”, or sometimes due to defective endometrial receptivity [29]. The

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prevalence of myomas in infertile patients is 5-10%, but when other causes of infertility are excluded, fibroids are found as the sole possible aetiology in only 1-2% of patients [30, 31]. When infertility is attributable to UF (type 3-5 intramural fibroids > 3 cm) in patients desiring to procreate using assisted reproductive techniques, a currently proposed algorithm [25, 29] includes medium-term therapy with GnRH antagonists ± ABT together with Controlled Ovarian Stimulation (COS) and Freezing, followed by the subsequent phase: in case of good response, it is possible to proceed directly to embryo transfer, while in case of insufficient response, surgical approach may still follow [25].

Finally, preliminary experiences from some of the authors report benefits of continuing combined GnRH antagonist therapy after myomectomy in the presence of other minor fibroids, both to prevent recurrence of HMB (Heavy Menstrual Bleeding) and/or other symptomatology and to preserve future fertility, although these are preliminary results requiring further studies for validation [32].

CLINICAL UTILIZATION OF GNRH ANTAGONISTS (± ABT) IN THE LONG-TERM (FROM 6 MONTHS ON)

Despite being a benign pathology, the symptomatology of UFs can have a strong impact on women's lives and women’s needs, problem and expectations [16]. UFs still today are often treated with demolitive surgery and drugs with low efficacy such as oral contraceptives (OCs) as testified by a very recent Italian survey [1]. Combined Oral Contraceptives (COCs) are often used in the treatment of UFs, but most of them can provide estrogen levels above the “ideal” estrogenic threshold which explains their partial long-term efficacy [11]. In the case of the fixed combination with relugolix + ABT, effective contraception is assured to patients after the first treatment cycle [33], while also ensuring an estrogenic balance suited to the concept of “therapeutic window” that needs to be established and maintained over time in this estrogen-dependent pathologies. This concept is confirmed by the fact that the venous thromboembolism risk of relugolix-CT is lower than that of traditional COCs [34].

For long-term management of moderate to severe UFs symptomatology, the most indicated use is that of GnRH antagonists ± ABT as described in the registration RCTs.

In particular, the following categories can be identified:

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- The perimenopausal patient (> 45 years) who in the past was often treated with surgical removal of the uterus in cases of severe menometrorrhagia symptoms, can now be accompanied to menopause with long-term medical therapy [26, 35].
- In perimenopause, menometrorrhagic phenomena are frequently found for multiple causes, such as ovulatory dysfunction, endometrial changes, possible coagulopathy, concomitant therapies or even possible structural conditions such as polyps, adenomyosis, leiomyoma, neoplasia/hyperplasia [35].

Once the primary underlying cause of abnormal uterine bleeding (AUB) is clarified, treatments aim to restore a regular bleeding pattern or achieve amenorrhoea. While in many cases treatment with progestins alone, either orally or with levonorgestrel-medicated IUDs (IntraUterine Devices), or even with COCs is applicable, in the case of menometrorrhagia caused by UFs, the resulting AUB/HMB has its own specific causes such as alterations in myometrial contractility, factors of altered paracrine signalling (growth factors, prostaglandins, endothelin, angiogenic factors) and haemostasis (alteration in the expression of coagulation factors and impairment of platelet action) in the endometrium. All of them are complex phenomena, sometimes still poorly understood, requiring a specific approach [35]. An extensive review argues, for example, that the use of progestins to manage fibroids (and fibroid-related HMB) is “like constantly adding gasoline to the fire” since progesterone is heavily involved in the pathogenesis [36].

GnRH antagonists (mandatory with ABT in case of long-term treatment) have demonstrated very effective reduction of moderate to severe heavy uterine bleeding in women with UFs, starting from the first cycle of use with response rates up to 60%, rising to levels of 80-90% with prolonged use, and amenorrhoea rates of 70-90% [18, 23, 37-39], as underlined by current indications.

But for how long can these patients be treated? The RCT trials of the new oral antagonists ± ABT were designed with follow-up of up to two years of treatment to ensure, in addition to efficacy on symptoms, safety for patients with long-term use. According to European regulatory bodies, if a drug is intended to be administered for a prolonged period, clinical studies must include extended exposure to the drug to evaluate its safety and efficacy over time, in line with ICH (International Council for Harmonisation) guidelines, and for this reason the clinical development studies of the

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new GnRH antagonists ± ABT have ensured extended follow-up [37, 38] up to two years, thus indicating that the optimal balance achieved can be used long-term.

Even Note 51, which governs the reimbursability of these drugs in Italy, indicates that additional cycles beyond two years for relugolix and one year for linzagolix can be evaluated at the clinician's discretion (AIFA Note 51). In summary, "long duration" is not a term rigidly defined as a fixed number of months or years but is related to the consistency of the clinical evidence produced and the specific therapeutic indication.

Real-world experiences of the long-term use up to 12 months are showing effectiveness and tolerability for managing symptomatic uterine fibroids [40].

The patient who cannot or does not want to undergo surgery, in whom continuous medical therapy is the primary option to allow adequate management of symptomatology and restore quality of life [41], treating the patient and not "just" the fibroid [16].

Patients may also have concomitant benign, estrogen-dependent gynaecologic conditions, such as adenomyosis and endometriosis, both of which are highly prevalent among women of reproductive age. Adenomyosis is estimated to affect approximately 12% [42, 43] of women, whereas endometriosis affects approximately 10% [44]. On the other hand, we know that 70 out of 100 women will receive a diagnosis of UFs by the age of 50 [45]. Gynaecological clinical practice demonstrates that these benign pathologies very frequently coexist. Epidemiological data confirm this: in a cohort of more than 1,000 patients with adenomyosis and other concomitant uterine pathologies, fibroids represent the most frequent concomitant condition (43%) [46]. Moreover, it is well known that there are high percentages of coexistence of adenomyosis and endometriosis, about 42% [47].

Both uterine fibroids and adenomyosis and endometriosis share as a common pathogenetic substrate, albeit with very different aetiologies, they are all estrogen driven pathologies; therefore, their growth is stimulated by estrogens, and re-establishing a stable and fixed estrogenic threshold can resolve the major symptomatology reported by patients [43, 48, 49].

A recent subanalysis of the relugolix combination therapy registration RCTs focused on evaluating the results of this treatment in the subgroup of patients (18.2%; 111 patients) who had a baseline diagnosis of adenomyosis, in addition to UFs and HMB. In this subgroup, as many as 83.8% in the

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group treated with relugolix combination therapy responded to treatment, with amenorrhoea rates of 65%, demonstrating that efficacy results in women with adenomyosis and UFs were comparable to the group with fibroids alone [50]. Moreover, benefits on dysmenorrhoea, chronic pelvic pain and menstrual bleeding have been recently reported in patients with adenomyosis and concomitant UFs [51]. Clinical experiences of using GnRH antagonists alone in patients with adenomyosis are also beginning to grow and appear encouraging [37, 52-54]; however, one must always consider balancing the profound hypoestrogenism that GnRH antagonists alone would entail in such patients and which would make long-term treatment impossible without ABT.

Could the patient who has already undergone surgery, in those cases where residual fibroids remain or significant menometrorrhagic symptomatology reappears, or to avoid recurrences, be a candidate for long-term treatment? The appearance of new fibroids (or recurrence) after non-radical surgical intervention is in fact described in a variable percentage ranging from 16% up to 60% [15, 55], since simple enucleation of the fibroid does not eliminate the underlying hormonal imbalance that can over time lead to new myomatous neoformations. Patients undergoing radiofrequency myolysis for G3-G4 symptomatic uterine fibroids, may also benefit from extending medical treatment the first months following the procedure as it maintains symptomatic control while the full ablative effect of the treatment establishes. These promising opportunities will need to be confirmed by prospective studies. At present, the new oral GnRH antagonists have a role in therapy and not in secondary prevention, although a retrospective Italian study observed a limited sample of patients in whom, even in the postoperative period [32], due to the presence of a fibromatous uterus and/or additional myomas, medical therapy was administered to prevent bleeding recurrence, with a partial response after 3 cycles (30%) and total response (100%) after 6 cycles. However, experience on the value of treatment with GnRH antagonists ± ABT in patients who have already undergone surgery is very limited, and further studies in larger prospective studies are absolutely necessary to evaluate the real efficacy and be able to recommend its use for possible long-term use after fibroid surgery.

DISCUSSION

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This new category of drugs, namely GnRH antagonists ± ABT, more than 5 years after their first authorization, has already gathered a considerable amount of clinical use experience, which makes it possible to outline several optimal clinical lines of use.

In the management of symptomatic UFs, the approach of starting with medical therapy is already confirmed as valid. Fortunately, in recent years, new drugs, such as GnRH antagonists ± ABT, have become available to gynaecologists for the treatment of symptomatic UFs, which are estrogen-dependent conditions.

Therefore, in the short/medium term, medical treatment with GnRH antagonists ± ABT has been demonstrated to be relevant, also evaluating it in synergy/alongside surgery, as already known for agonists. But these new combinations have overcome the disadvantages related to the agonists' mode of administration and the flare-up effect.

It is in the long term, however, that these combinations represent the optimal solutions for various categories of patients, according to the estrogenic threshold to be maintained in a stable and consistent manner in women affected by estrogen-dependent diseases [13]. This treatment also improves women's quality of life, as well as in cases of concomitant benign uterine pathologies, such as adenomyosis or endometriosis, which are also estrogen-dependent conditions.

An important consideration, particularly in long-term treatment, is the appropriate balance between efficacy and safety. With regards to bone health, even a short-term total blockade (3 months) of the hypothalamic-pituitary-ovarian system leads to hypoestrogenism with a subsequent reduction in bone mineralization, which can be challenging to reverse [17, 18].

Balance can be maintained by combining an adequate ABT with the antagonist, within the so-called therapeutic window: bone is in fact an organ sensitive to extremely low estrogenic dosages (20 pg/ml), while fibromatous cells, as well as endometriotic cells, respond to much higher estrogenic dosages (50-60 pg/ml) [13].

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CONCLUSIONS

The extensive clinical experience gained over the years in the pharmacological treatment of symptomatic UFs with GnRH antagonists ± ABT allows us to place high confidence in this class of

drugs for a personalized therapy of women affected by this widely prevalent condition. These drugs can be used in the short, medium, and long term. Where the clinical need is a rapid volume reduction, the use of the antagonist alone may be indicated, while in the medium and long term, the combination with ABT is indispensable. Nowadays, with the advantages of these pharmacological options available, the use of agonists should be considered outdated. In the coming years, as suggested by our published preliminary experiences, additional clinical applications may emerge, including use as a bridging option while awaiting the results of minimally invasive procedures (such as uterine fibroid radiofrequency ablation) and the potential prevention of fibroid recurrence.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

All authors contributed equally to conceptualization, project administration, supervision, writing – original draft, writing – review & editing.

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Study registration

N/A.

Disclosure of interests

K.L.A. is advisory board for Gedeon Richter and Bayer consultant for Theramex. S.A. has served as speaker/consultant for Gedeon Richter, Theramex, AGPharma, Italfarmaco, Exeltis, Organon. A.D.S.S. serves as a consultant and on an advisory board (compensated) for Theramex, Gedeon Richter, Bayer, Medtronic and Storz. A.M. serves as a consultant for Gedeon Richter and for Theramex. L.M. serves as a consultant for Gedeon Richter and Theramex. M.V. serves as a consultant and on an advisory board (compensated) for Theramex, Gedeon Richter, Bayer, Exeltis. L.N. declares no conflict of interests.

Ethical approval

N/A.

Informed consent

N/A.

Data sharing

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