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Medical management of fibroids

Srividhya Sankaran MRCOG

Clinical Fellow in Obstetrics and Gynaecology

Isaac T. Manyonda* BSc, PhD, MRCOG

Consultant in Obstetrics and Gynaecology

St George's Hospital NHS Trust, Department of Obstetrics and Gynaecology, Blackshaw Road, London SW17 0QT, UK

The ideal medical therapy for fibroids is, arguably, a tablet that is taken by mouth, once a day or, even better, once a week, with minimal, if any, side-effects, that induces fibroid regression and thus a resolution of symptoms rapidly, but without affecting fertility. Such a magic bullet does not yet exist, and there are no indications that one is on the horizon. Driven by the observation that fibroid growth is hormone dependent, current medical treatments mainly involve hormonal manipulations. Gonadotrophin-releasing hormone analogues (GnRHa) have been the most widely used, and while they do cause fibroid regression, they can only be used in the short term, as temporizing measures in the perimenopausal woman, or pre-operatively to reduce fibroid size, influence the type of surgery, restore haemoglobin levels and apparently reduce blood loss at operation. They are notorious for rebound growth of the fibroids upon cessation of therapy, and have major side-effects. GnRH antagonists avoid the initial flare effect seen with GnRHa therapy, but otherwise do not appear to have any additional advantages over GnRHa. Selective oestrogen receptor modulators, such as raloxifene, have been shown to induce fibroid regression effectively in post-, but not pre-, menopausal women; even in the former group, experience with these drugs is limited, and they are associated with significant side-effects. Aromatase inhibitors only appear to be effective in postmenopausal women, have potentially significant long-term side-effects, and experience with their use is also limited. There are suggestions that the levonorgestrel intra-uterine system can cause dramatic reduction in menstrual flow in women with fibroids, but to date there have been no RCTs of its use in these women, in whom rates of expulsion of the device appear to be high. The progesterone antagonists mifepristone and asoprisnil have shown significant promise and warrant further research, as they appear to show efficacy in inducing fibroid regression without major side-effects. However, they and the other hormonal therapies that alter oestrogen and progesterone production or function significantly (danazol, gestrinone) are not compatible with reproduction. Therefore, the quest for the ideal medical therapy for fibroid disease continues, and increasing

* Corresponding author. Tel.: +44 (0) 208 725 3663; Fax: +44 (0) 208 725 5958.

E-mail address: imanyond@sgul.ac.uk (I.T. Manyonda).

understanding of fibroid biology is ushering in non-hormonal therapies, although all are confined to laboratory experimentation at present. In the meantime, surgical and radiological approaches remain the mainstay effective therapies.

Key words: leiomyoma; uterine fibroids; hormones; gonadotrophin-releasing hormone analogues; oestrogen; progestogen; raloxifene; tamoxifen; mifepristone; asoprisnil; progesterone receptor modulators; oestrogen receptor modulators; add-back.

Fibroids are the most common tumours in women of reproductive age. They are symptomatic in 50% of cases, with the peak incidence of symptoms occurring among women in their 30s and 40s.¹ Symptoms include menstrual disturbance, commonly menorrhagia and dysmenorrhoea; pressure symptoms such as increased urinary frequency, pelvic pain and constipation; and they may interfere with reproduction. Although it is usually assumed that problems associated with fibroids resolve with the onset of the menopause, in reality, fibroids can cause symptoms, including abnormal bleeding, even during the menopause. In a British series describing long-term follow-up of women undergoing uterine artery embolization (UAE), for instance, almost one in five women was aged 50 years or older at the time of the procedure.² Thus, although benign, fibroids have a major impact on women's health and their quality of life.

As recently as 15–20 years ago, the choices for women with symptomatic fibroids were confined to abdominal hysterectomy and conventional abdominal myomectomy. The former constituted a 'cure', as all symptoms were eradicated without a possibility of recurrence of the fibroids, but hysterectomy is unacceptable to women wishing to retain fertility potential. Myomectomy is a major operation with associated morbidity and indeed mortality risks. It may compromise the very same fertility that it seeks to preserve due to the potential for adhesion formation, and there is a significant risk of recurrence of the disease. In recent years, a multitude of additional therapeutic choices have emerged, including laparoscopic and vaginal myomectomy^{3,4}, UAE⁵ and, more recently, magnetic-resonance-guided focused ultrasound surgery (MRgFUS).⁶ However, it is abundantly clear that none of these therapies is a panacea. Laparoscopic surgery requires skills that are not commonplace, and there are limitations on the size and number of fibroids that can be treated by this modality. Much the same applies to vaginal myomectomy. UAE is now widely used in the USA and Western Europe, and has been recommended by the UK's National Institute for Clinical Excellence (NICE) as an alternative therapy to hysterectomy. However, it is still under evaluation, has a range of complications including premature ovarian failure, chronic vaginal discharge and, in rare cases, pelvic sepsis, and may have limited efficacy where the fibroids are large. Although there are a number of reports of successful pregnancy following UAE⁷, experience is limited and research is required in this area. The newer treatment MRgFUS was approved by the US Food and Drug Administration (FDA) in 2004⁸, while NICE has recommended that the procedure should be used in an audit and research setting.⁹ While these treatments have varying degrees of efficacy, they all have major cost implications. MRgFUS, for example, requires the availability of costly 'open' magnetic resonance imaging facilities that many units do not have, while the costs of other procedures including myomectomy and hysterectomy are well reported in the literature.

Given the choice, many women would opt to avoid major surgery such as myomectomy or hysterectomy, or indeed even the less invasive procedures such as UAE or MRgFUS. There is clearly a need for medical therapy that eliminates the need for

surgery, is relatively cheap, and has efficacy that is equivalent or superior to surgery. At present, such medical therapy does not exist, but research is ongoing and promising avenues are opening up. Most of the current medical therapeutic approaches exploit the observations that uterine fibroids have significantly increased concentrations of both oestrogen and progesterone receptors (ORs and PRs) compared with normal myometrium^{10,11}, and that ovarian steroids influence fibroid growth. Most available therapies are therefore hormonal or act on the relevant hormones or their receptors to interfere with fibroid growth. However, as knowledge of fibroid biology increases, non-hormonal therapies are likely to emerge that target aspects of fibroid growth in a non-hormonal way; indeed, laboratory tests of such agents are underway already.

INDICATIONS FOR MEDICAL THERAPY

At present, medical treatments are only used for short-term therapy because of the significant risks with long-term therapy, or lack of evidence regarding the benefits and risks of long-term therapy with the newer medical agents. They may be used or are used in the following situations:

- as 'stand-alone' treatment for temporary relief of symptoms for short periods. This application is suitable in women with symptomatic fibroids in the perimenopausal years or in patients not suitable for surgery due to medical reasons;
- as a pre-operative adjunct to reduce the size of fibroids, to control bleeding and to improve haemoglobin levels. The reduction in fibroid size may also convert a technically difficult procedure to an easier procedure (e.g. abdominal hysterectomy to vaginal hysterectomy). They can be used before myomectomy, hysterectomy and hysteroscopic submucous resection of fibroids. At present, gonadotrophin-releasing hormone analogues (GnRHa) are mainly used for this purpose; and
- in research, as part of an evaluation of new potential therapies.

AVAILABLE MEDICAL AGENTS

While there are no agents that could be described as definitive stand-alone treatments for fibroid disease, there is a wide range of agents that are used in aspects of the management of this common tumour. Thus, GnRHa, alone or more commonly with 'add-back therapy', are frequently used as temporizing measures in perimenopausal women, or pre-operatively to reduce fibroid size and render surgery safer/easier. Selective oestrogen receptor modulators (SERMs), antiprogestins (RU486 and asnoprisinil), aromatase inhibitors, carbegoline, danazol and gestrinone are potential agents that have been used to varying degrees. The increasing knowledge of the biology of uterine fibroids is stimulating the development of newer non-hormonal therapies. The ultimate goal must be the development of an agent that induces fibroid regression without interfering with the ovulatory menstrual cycles, has minimal side-effects and is economical.

GnRH analogues

Gonadotrophin-releasing hormone (GnRH) and GnRHa have been used extensively in clinical medicine since they were identified and synthesized in the 1970s. There are more than 2000 GnRHa with agonistic and antagonistic actions, and many have

been evaluated for the treatment of a wide range of conditions that require temporary and reversible suppression of gonadotrophin secretion. In gynaecological practice, they have been used in the treatment of diverse disorders including endometriosis, hirsutism, dysfunctional uterine bleeding and premenstrual syndrome, and in assisted reproduction. They are also used extensively in some hormone-dependent tumours such as prostatic cancer. Their use in fibroid disease was first evaluated in the late 1980s.

Mechanism of action

Native GnRH is a decapeptide which is produced and released in a pulsatile fashion from the arcuate nucleus and pre-optic anterior hypothalamic area. It reaches the anterior pituitary through the portal system and is believed to bind to specific receptors in the anterior pituitary, where it stimulates the synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in both men and women.¹² GnRH is rapidly degraded by peptidase and cleared by glomerular filtration. Its half-life in the peripheral circulation is 2–4 min.¹³ To increase the potency and duration of GnRH, analogues with agonistic or antagonistic properties have been synthesized and are available for clinical use (Table I). GnRH agonists have greater potency and a longer half-life than native GnRH. Their potency and activity is determined by amino acid substitutions; thus, substitution of an amino acid at the 6 or 10 position results in analogues with agonistic activity, whereas modification at the 2 or 3 position results in analogues with antagonistic properties. The deletion of an amino acid at the 10 position also increases the binding affinity of GnRHs.

A single injection of GnRHs produces an initial stimulation of pituitary gonadotrophins, resulting in increased secretion of FSH and LH and the expected gonadal response. However, continuous or repeated administration of GnRHs in a continuous (non-pulsatile) fashion or administration of supraphysiological doses ultimately produces inhibition of the pituitary–gonadal axis. Functional changes resulting from this inhibition include pituitary GnRH receptor downregulation, decreased gonadotrophin secretion, decreased steroidogenesis and gametogenesis. These inhibitory effects of GnRHs are fully reversible. Evidence from animal models suggests that GnRHs may

Table I. Gonadotrophin-releasing hormone agonists studied for gynaecological conditions.¹⁰⁸

Generic name	Route of administration	Dose regimen
Buserelin	Subcutaneous	200 µg/day
	Intranasal	300–344 µg × 4 days
Decapeptyl	Intramuscular depot	3 mg/month
Goserelin	Subcutaneous implant	3.6 mg/month
		10.8 mg/3 months
Histerelin	Subcutaneous injection	100 µg/day
Leuprolide	Subcutaneous injection	500–1000 µg/day
	Intranasal	400 µg × 4 days
	Intramuscular depot	3.75–7.5 mg/month
		10.25 mg/3 months
Nafarelin	Intranasal	200 µg × 2 days
	Intramuscular depot	3 mg/month
Tryptorelin	Intramuscular depot	2–4 mg/month

also act directly on extrapituitary reproductive and non-reproductive target sites, such as the gonads, uterus and prostate.^{12,13} However, no documented evidence shows that GnRHa have this effect in humans.

Pharmacokinetics

GnRHa cannot be administered orally because they are readily destroyed by the digestive process, but they may be given parenterally, by nasal spray or as vaginal pessaries. The biological efficacy of GnRHa administered through nasal spray is only 2–5% of that achieved by the subcutaneous route. GnRHa-containing implants that are capable of slow drug release have been developed to avoid frequent injections. The peptide drug is released from the depot formulations at a functionally constant daily rate for 1, 3 or 4 months, depending on the polymer type (polylactic/glycolic acid for a 1-month depot and polylactic acid for a depot of >2 months), with doses ranging between 3.75 and 30 mg. Recently, an implant that delivers leuprorelin for 1 year has been evaluated. Local reactions are more common after application of the 3- or 4-month depot in comparison with the 1-month depot.¹⁴

Fibroid shrinkage: mechanisms

GnRHa undoubtedly induce fibroid tumour shrinkage, the degree of which has been shown to be inversely proportional to the percentage of cells that are OR positive, thus implicating oestrogen as a major effector of tumour growth and its reduction as the central mechanism of fibroid shrinkage with GnRHa therapy.¹⁵ Chegini et al found evidence of suppression of signal transduction pathways involving growth factors, ovarian steroids and adhesion molecule with a resulting decrease in DNA synthesis, cell proliferation and production of transforming growth factor- β .^{16,17} They found that medical treatment causes altered regulation in a number of genes involved in regulation of cell growth, signal transduction, transcription factors and cell structures.¹⁸ Therapy with leuprolide acetate has been associated with hyalization of leiomyomata¹⁹ and decreases in uterine or tumour arterial size and blood flow variables.^{20–22}

Use of GnRHa as stand-alone therapy

All trials of all types of GnRHa, randomized or otherwise, and all systematic reviews of trials have reported that GnRHa reduce uterine and fibroid volume significantly from baseline compared with placebo or no treatment. They improve fibroid-related symptoms such as menorrhagia, even inducing amenorrhoea in some women depending on the duration of use, and facilitate the restoration of haemoglobin levels.^{23–27} However, there are significant adverse effects, most importantly a reduction in bone mineral density and the development of menopause-type symptoms of oestrogen deficiency, both of which limit the standard use of GnRHa to 6 months.²⁸ Moreover, the regression of uterine/fibroid volume is not permanent, with fibroids returning to their original size or even enlarging more rapidly upon cessation of therapy.²⁹ Having said that, half of women with abnormal bleeding attributed to leiomyomata uteri had sustained benefits for up to 6 months after leuprolide acetate therapy, suggesting that the benefits of leuprolide acetate in controlling symptoms may persist after therapy despite a return of the uterus to pretreatment size.³⁰

GnRHa with add-back therapy

On the one hand, GnRHa are powerful drugs with high efficacy, while on the other hand, their side-effects of menopausal symptoms are debilitating and their impact on bone loss cannot be overlooked. 'Add-back regimens' have emerged as a way of counteracting the unwanted effects, while retaining the benefits of GnRHa therapy. The concept is now well established, and in current practice, it would be unusual to administer GnRHa for more than 3 months without add-back therapy. A variety of agents are used including tibolone, raloxifene, progestogens alone, oestrogens alone, and combined oestrogens and progestogens. A significant concern in the early use of add-back therapy was whether the latter would compromise the efficacy of GnRHa. Interestingly, many well-informed patients often enquire about this when GnRHa are prescribed to treat endometriosis (personal observation). There is now ample evidence that the use of add-back therapy does not compromise the efficacy of GnRHa. The fundamental aim of add-back therapy is to ameliorate the menopausal symptoms and prevent bone loss; there are subtle differences in the extent to which these aims are achieved when using different add-back regimens, and it is therefore worth briefly exploring the available evidence.

Tibolone

This is the authors' preferred add-back agent, partly because in conventional hormone replacement therapy, it is reportedly associated with preservation of energy and libido, can be given to women who do not need withdrawal bleeds, and eradicates most of the symptoms of oestrogen deficiency. In the treatment of fibroid disease, tibolone has also been the subject of the largest number of randomized clinical trials (RCTs) in which its efficacy has been demonstrated. The first prospective, randomized, double-blind, placebo-controlled, clinical trial comparing 6 months of treatment with leuprolide acetate (3.75 mg every 28 days IM) combined with daily placebo tablets or with tibolone 2.5 mg/day concluded that administration of tibolone in association with GnRHa reduces vasomotor symptoms and prevents bone loss, without compromising the therapeutic efficacy of GnRHa alone.³¹ Similar results were confirmed by other RCTs.^{32,33} Long-term administration of GnRHa plus tibolone for 24 months reduces hot flushes and prevents bone loss without changing the lipid profile.³⁴

Raloxifene

An RCT which compared GnRHa plus raloxifene with GnRHa plus placebo for 6 months found that both treatments induced a reduction in both uterine and fibroid size from baseline, but that GnRH plus raloxifene caused a significantly greater reduction in fibroid size at 6 months compared with GnRHa plus placebo. Thus, it seems that raloxifene acted synergistically with GnRHa to cause more pronounced fibroid regression. GnRHa plus raloxifene caused a significant reduction in bone mineral density loss. No significant difference was noted in fibroid-related symptoms, cognition, mood and overall quality of life or menopausal symptoms.³⁵⁻³⁷ In an observational study using leuprolide acetate depot 3.75 mg every 28 days and raloxifene hydrochloride 60 mg/day for 18 cycles, no significant change in bone mineral density or in any bone metabolism markers was observed. A significant decrease in uterine and leiomyoma sizes was detected in comparison with baseline after 6 months. No major adverse effects were reported.³⁸ To summarize, raloxifene does not ameliorate

menopausal symptoms of oestrogen deficiency when given as add-back therapy, but it significantly reduces bone loss and appears to act synergistically to reduce fibroid volume. Due to this failure to abrogate the debilitating menopausal symptoms of oestrogen deficiency, the authors would always choose tibolone over raloxifene as add-back therapy.

Progestogens

Medroxyprogesterone acetate (MPA) may be a useful adjunct to GnRHa in women with fibroids, reducing side-effects and possibly prolonging the response, although positive effects on bone density have yet to be confirmed. There is no evidence that MPA prevents the regrowth of uterine volume after GnRHa therapy is stopped. Small RCTs found that GnRHa plus MPA reduced the proportion of women with vasomotor symptoms. The optimum administration regimen remains to be clarified.^{30,39–42}

Oestrogens

Oestrogens are not routinely used alone because of the risk of endometrial hyperplasia with unopposed oestrogen therapy. Oestrinol, a weaker and short-acting oestrogen, has been evaluated as an add-back therapy in a small trial involving 12 patients. This trial found that there was a reduction in uterine volume without bone loss in the group of patients who received oestrinol plus GnRHa compared with the group of patients who received GnRHa alone.⁴³

Combined oestrogens and progesterones

An RCT compared GnRH plus combined oestrogens and progesterones (low-dose continuous oestropipate plus cyclic norethindrone) with GnRH plus progestogen alone (higher dose norethisterone), and found that the mean uterine volume was reduced in those taking combined oestrogens and progesterones as add-back therapy. No differences were reported in hypo-oestrogenic symptoms or the return of uterine volume to baseline levels 6 months after treatment.^{44,45}

Use of pre-operative GnRHa therapy

This issue has been addressed in another chapter in this volume (Conventional myomectomy), but its importance is such that it warrants reiterating here. A Cochrane Database Systematic Review⁴⁶ to evaluate the role of GnRHa prior to either hysterectomy or myomectomy showed that pre- and postoperative haemoglobin and haematocrit were improved significantly by the use of GnRHa prior to surgery. Uterine volume and size, fibroid volume and pelvic symptoms were all reduced. Hysterectomy was rendered easier, with reduced operating time, and a greater proportion of hysterectomy patients were able to have a vaginal rather than an abdominal procedure. Blood loss and rate of vertical incision were reduced for both myomectomy and hysterectomy. Duration of hospital stay was reduced. Change in postoperative fertility could not be assessed due to the lack of data.

The disadvantages of GnRHa include cost, menopausal symptoms and, with prolonged therapy, bone demineralization. Pre-operative use of GnRHa has been reported as a risk factor for recurrence of fibroids⁴⁷, presumably because smaller fibroids shrink and are ignored at the time of surgery, only to regrow when the effects of GnRHa wear off. However, the Cochrane Review found equivocal evidence for this.⁴⁶ In

a series of 426 women who underwent laparoscopic myomectomy, Dubuisson et al reported that 11.3% were converted to open procedures, and the pre-operative use of GnRHa was one of four factors identified which were independently related to the risk of conversion.⁴⁸ A problem frequently encountered in clinical practice, but poorly researched, is that GnRHa render surgical planes less distinct, perhaps due to softening of the fibroids, which makes enucleation more difficult.⁴⁹ This might account for the significantly longer operative time for laparoscopic myomectomy associated with pre-operative GnRHa use⁵⁰, and may also explain Dubuisson et al's finding that the risk of conversion from laparoscopic to open myomectomy is increased in association with pre-operative GnRHa use.⁴⁸ In a recent retrospective study, Seracchioli et al performed laparoscopic myomectomy for fibroids penetrating the uterine cavity without the use of GnRHa.⁵¹ Although their findings are encouraging in terms of feasibility and safety of surgical technique, length of operation and blood loss, the numbers are too small to draw any useful conclusions about obstetric outcome (nine pregnancies out of 34 cases, seven of which went to full term without complications). Finally, a review of the cost-effectiveness of GnRHa found that the costs outweigh its benefits.⁵² In low- and middle-income countries, the cost of using GnRHa and UAE may be prohibitive (especially where there is out-of-pocket payment).⁵³

Thus, the debate on the place of GnRHa in pre-operative therapy will continue, and undoubtedly more research is required in this area. To inject a personal angle, the authors rarely use GnRHa prior to conventional abdominal myomectomy, and the reasons can be summarized as follows:

- large and multiple fibroids (level of the umbilicus and beyond) show minimal regression in response to GnRHa therapy;
- the use of GnRHa has not been shown to be cost-effective;
- GnRHa have significant menopausal side-effects;
- the authors' experience indicates that fibroid enucleation is compromised by destruction of tissue planes consequent upon use of GnRHa;
- it is teleologically sound to suppose that the use of GnRHa increases the risk of recurrence since smaller fibroids regress and are left behind at the time of myomectomy, only to re-grow aggressively when GnRHa is withdrawn after surgery; and
- the authors find no evidence for a reduction in intra-operative blood loss as a result of the use of GnRHa, while the techniques used to reduce blood loss (vasopressin and tranexamic acid) are effective and cheaper.

However, there are some circumstances in which the authors would use GnRHa:

- women in whom it is important to have a good pre-operative haemoglobin, such as Jehovahs' Witnesses, or women who are severely anaemic and where simpler measures to build up the haemoglobin have failed; and
- women with submucous fibroids of greater than 4-cm diameter where access into the uterine cavity to carry out resection might be compromised. The authors do not use GnRHa to reduce blood loss at resection of smaller fibroids because intramyometrial injection of vasopressin renders the surgical field dry.

It should also be pointed out that an RCT⁵⁴, subsequent to the Cochrane Review, was unable to demonstrate any difference in the amount of blood loss at surgery, duration of surgery, postoperative morbidity or hospital stay between women who

received pre-operative GnRHa therapy and those who did not. Furthermore, it was not possible to demonstrate any difference in cleavage planes among treated and untreated myomas; a claim made consistently by the authors and other opponents of GnRHa pretreatment.

GNRH ANTAGONISTS

The US FDA has approved the GnRH antagonists abarelix (Plenaxis), cetrorelix (Cetrotide; both Serono) and ganirelix (Antagon; Organon International) for clinical use. These agents are used as injectables, usually at doses of 5 mg twice daily for the initial 2 days followed by 0.8 mg twice daily for at least 3 months. GnRH antagonists directly inhibit reproductive processes by competing for and occupying pituitary GnRH receptors, thus blocking the access of endogenous GnRH and exogenously administered agonists to their required recognition site.⁵⁵ Thus, in contrast to GnRH agonists, the antagonists immediately suppress pituitary gonadotropins and thereby allow flexibility in the degree of pituitary–gonadal suppression. Discontinuation of GnRH antagonist treatment leads to a rapid and predictable recovery of the pituitary–gonadal axis.⁵⁶ Earlier formulations were associated with transient systemic and local reactions associated with histamine release, but the more recent preparations are better tolerated and have fewer side-effects.⁵⁷

Most experience with GnRH antagonists is in assisted reproduction and prostate cancer therapy, where they have largely been found to be as effective as established therapies.⁵⁸ There are no RCTs of their use in fibroid disease therapy, but observational studies on small numbers of patients suggest beneficial effects.^{59,60} Daily treatment with ganirelix 2 mg resulted in rapid reduction of leiomyoma and uterine volume in premenopausal women with minor side-effects.⁶¹ If longer-acting GnRH antagonists become available, pretreatment with GnRH antagonists should be preferred over GnRH agonists prior to surgery.

SELECTIVE OESTROGEN RECEPTOR MODULATORS

SERMs are most commonly used in the treatment and prevention of oestrogen-receptor-positive carcinoma of the breast, well-known examples being tamoxifen and raloxifene. They are non-steroidal OR ligands that act as oestrogens in some tissues while blocking oestrogen action in others.

Mechanism of action

Although the exact mechanism of action of SERMs has yet to be fully elucidated, it has been hypothesized that these agents work by inducing conformational changes in the OR, which results in differential expression of specific oestrogen-regulated genes in different tissues.⁶² The individual characteristics of the different SERMs are determined by their structure, the type of OR they bind to, and the set of molecules that interact with the OR–SORM complex in a given cell. This, in turn, determines whether the SORM exhibits agonistic or antagonistic activity.⁶³ For example, raloxifene maintains beneficial oestrogenic activity on bone and lipids, and anti-oestrogenic activity on endometrial and breast tissue⁶⁴, while tamoxifen acts as an OR agonist in the uterus and bone, and as an antagonist in the mammary gland.⁶³

Pharmacokinetics

Oral administration of raloxifene results in rapid absorption with absolute bioavailability of about 2%.⁶⁴ Although it undergoes extensive systemic biotransformation, it does not appear to be metabolized by the cytochrome P450 pathway. It has a long plasma half-life of up to 27 h which is due to the drug's reversible systemic metabolism and significant entero-hepatic cycling. As raloxifene is eliminated primarily in faeces and only a minimal amount is found in urine, dosage adjustments are not required in patients with renal insufficiency.⁶⁴

SERMs in the treatment of fibroids

Any molecule that blocks oestrogen activity has the potential for therapeutic activity against fibroids, since oestrogen is known to influence fibroid growth. SERMs are therefore within this category of molecule. However, because of its endometrial hyperplastic effect and case reports of fibroid growth following treatment, the potential of tamoxifen in the treatment of fibroids has not been investigated in RCTs. Raloxifene, on the other hand, has shown promise. A 60 mg daily dose has been shown to reduce fibroid volume for up to 1 year, but only in postmenopausal women.⁶⁵ Premenopausal women given the same treatment did not respond⁶⁶, even when higher doses (180 mg/day) of raloxifene were used. The explanation may simply be that raloxifene is able to counteract the low concentrations of background oestradiol seen in postmenopausal women, but not the higher concentrations in premenopausal women.⁶⁷ Although another RCT of raloxifene in older premenopausal women (mean age 40 years) showed a reduction in fibroid volume in the treated group compared with the untreated controls, the reduction was less than that seen with postmenopausal women, and the authors questioned the usefulness of raloxifene in premenopausal women.⁶⁸

Side-effects and risks

In the study of older premenopausal women⁶⁸, the treatment was generally well tolerated. Hot flushes, a typical side-effect of raloxifene, developed in one patient in the raloxifene group.⁶⁸ Other side-effects reported were increased appetite, weight gain, gastralgia and dry skin. No serious adverse events were recorded, and there were no discontinuations due to adverse events during the study course. Raloxifene treatment did not alter the hypophyseal–gonadal and thyroidal hormonal axis. However, leg pain must be taken seriously in women taking raloxifene, as the most serious adverse effect is the increase in venous thromboembolism. Leg cramps were reported by 4% of the women taking raloxifene. In the MORE study, the relative risk, compared with placebo, for a thromboembolic event was 3.1 (95% confidence interval 1.5–6.2).⁶⁹

In summary, although raloxifene appears to be promising, there is insufficient evidence to conclude that SERMs reduce the size of fibroids or improve clinical outcomes in premenopausal women. Studies to date have been of poor design and numbers have usually been too small to allow any useful conclusions. In addition, the safety of SERMs used in this way is uncertain, and they should be used with caution.⁷⁰

AROMATASE INHIBITORS

Aromatase inhibitors markedly suppress plasma oestrogen levels in postmenopausal women by inhibiting or inactivating aromatase, the enzyme which catalyses the

synthesis of oestrogens from androgenic substances such as androstenedione.⁷¹ Leiomyoma cells and subcutaneous fat cells express aromatase, and are therefore able to synthesize oestrogen. This observation may explain why fibroids do not always regress in postmenopausal women, and also suggests a possible therapeutic role for aromatase inhibitors in the treatment of symptomatic fibroids in premenopausal and menopausal women.⁷² To date, the use of aromatase inhibitors for the treatment of fibroid disease is confined to case reports. Kaunitz described the successful use of anastrozole, a third-generation non-steroidal aromatase inhibitor, in treating uterine bleeding associated with fibroids in an obese postmenopausal woman.⁷³ Anastrozole use was associated with a reduction in the size of the woman's dominant fibroid, thinning of her endometrium and cessation of bleeding. Japanese investigators have reported the successful use of an aromatase inhibitor, fadrozole, in reducing the dimensions of a fibroid tumour causing urinary retention in a perimenopausal woman. They reported a 71% reduction in fibroid volume in 8 weeks.⁷⁴

Anastrozole has a half-life of approximately 48 h and is effective with daily oral administration. Aromatase inhibitors are generally well tolerated with a low incidence of serious short-term adverse effects. The most common side-effects are hot flushes, vaginal dryness and musculoskeletal pain, and they are usually mild. Women taking aromatase inhibitors seem less likely to experience hot flushes and more likely to experience musculoskeletal pain than those using tamoxifen. In contrast to tamoxifen use, aromatase inhibitors do not increase the risk of endometrial neoplasia or thromboembolism. However, long-term use with the consequent hypo-oestrogenaemia could result in loss of bone mineralization and an increased fracture risk, making monitoring of bone density mandatory in women using this medication. Biphosphonate therapy is likely to be useful in such settings to counteract bone loss. Other possible long-term adverse sequelae of aromatase inhibitor use include cardiovascular disease and loss of cognitive function. However, at present, these considerations only apply when these substances are being used in the treatment of breast disease, and it seems unlikely that they will be used routinely in fibroid disease in the near future. The vast majority of women presenting with fibroid disease who would benefit from medical therapy are premenopausal, and aromatase inhibitors are unlikely to be effective. It should, however, be noted that in the obese menopausal woman presenting with fibroid disease, aromatase inhibitors may be preferable to progestin therapy as the latter has the potential to exacerbate the potential lipid disorder in the obese, often hypertensive woman.

LEVONORGESTEROL INTRA-UTERINE DEVICE

The levonorgestrel intra-uterine device (LNG-IUS) is effective in reducing menstrual blood loss and should be considered as an alternative to surgical treatment.⁷⁵ This system consists of a T-shaped intra-uterine device sheathed with a reservoir of levonorgestrel that is released at a rate of 20 µg/day. Hormone release at the target organ minimizes the systemic side-effects. It exerts its clinical effect by preventing endometrial proliferation, and consequently reduces both the duration of bleeding and the amount of menstrual loss.⁷⁶ Patients should be counselled regarding the irregular bleeding which can last from 3 to 6 months. Some women experience hormonal side-effects such as weight gain, breast tenderness and bloating, and the device is occasionally expelled spontaneously. The LNG-IUS has been shown to reduce menstrual blood loss by 94% by 3 months, and is well accepted by most women when used in the general population of women with menorrhagia.⁷⁷

In a landmark study of the LNG-IUS, Lahteenmaki et al randomized women on surgical waiting lists to continue with their current regimen or to use an LNG-IUS; 64% women using the LNG-IUS cancelled their surgery to continue using the LNG-IUS, compared with only 14% of women not using the LNG-IUS.⁷⁸ Other studies followed which showed that the LNG-IUS was a cost-effective alternative to hysterectomy during the first year.⁷⁹ Of a total of 236 women with menorrhagia, 119 were assigned at random to receive the LNG-IUS, and 117 to hysterectomy. In the LNG-IUS group, 20% had opted for a hysterectomy by 1 year while 68% continued to use the LNG-IUS. After 5 years of follow-up, 232 women (99%) women were analysed for the primary outcomes. The two groups did not differ substantially in terms of health-related quality of life or psychosocial well-being.⁸⁰ Although 50 (42%) of the women assigned to the LNG-IUS group eventually underwent a hysterectomy, the discounted direct and indirect costs in the LNG-IUS group remained substantially lower than in the hysterectomy group. Satisfaction with treatment was similar in both groups.⁸⁰ Of the 57 women with an LNG-IUS in situ at 5 years, 43 (75%) reported amenorrhoea or oligomenorrhoea, 11 (19%) reported irregular bleeding, and 3(6%) reported scanty regular bleeding.⁸⁰ The authors rightly concluded that by providing improvement in health-related quality of life at relatively low cost, the LNG-IUS may offer a wider availability of choices for the patient and may decrease cost due to interventions involving surgery. Compared with other medications, the LNG-IUS is much cheaper per menstrual cycle unless it is removed before 5 years. Therefore, long-term acceptability is essential.⁸¹

At present, there are no RCTs of use of the LNG-IUS in menorrhagic women with uterine myomas. There are, of course, reports of its use in these women, with striking reductions in menorrhagia being reported.⁸² Although some women with large intramural myomas had spontaneous expulsion of the LNG-IUS at various intervals, they wanted re-insertion of the device because of remarkable reduction in menorrhagia.⁸³ Significant increases in haemoglobin levels in blood were observed after insertion of the LNG-IUS, but no significant differences were noted in myoma volume and uterine volume, as assessed by magnetic resonance imaging between pretreatment and 12 months of use.^{82,83} There is therefore an obvious need for further research in this area.⁸⁴ It would be interesting to establish whether expulsion of the device is dependent upon the size, number or location of the fibroids; it is reasonable to assume that submucous fibroids, or large intramural fibroids distorting the cavity, are likely to be associated with an increased risk, but definitive studies need to be undertaken in order to provide the evidence base to better advise patients.

ANTIPIROGESTERONES

While it has long been established that oestrogen promotes fibroid tumour growth, recent biochemical and clinical studies have suggested that progesterone, progestins and PRs may also enhance proliferative activity in fibroids.⁸⁵ These observations have therefore raised the possibility that antiprogestins and PR agonists/antagonists could be useful in the medical management of uterine fibroids. The effects of progesterone on target tissues are mediated via PRs, which belong to the nuclear receptor family. PRs function as ligand-activated transcription factors to regulate the expression of specific sets of target genes. PR antagonists regress the biological actions of progesterone by inhibiting PR activation.

Mifepristone

Most readers will be familiar with mifepristone (RU 486) as the drug used for medical termination of pregnancy, with or without misoprostol. RU 486 is a high PR affinity antiprogesterin. For purposes of pregnancy termination, it is used in doses of 200–800 mg and its efficacy is well proven. Early reports of the use of RU 486 for the treatment of fibroids date back to 2002, when De Leo et al used doses ranging from 12.5 to 50 mg daily and reported a reduction in uterine/fibroid volume of 40–50%, with amenorrhoea in most subjects.⁸⁶ This report was corroborated by a paper 1 year later from a group who used RU 486 at a dose of 5 or 10 mg/day for 1 year, and found that it was effective in decreasing mean uterine volume by 50%, while amenorrhoea occurred in 40–70% of the subjects. Adverse effects included vasomotor symptoms, but no change in bone mineral density was noted. Hot flushes were increased over baseline in the 10-mg group, but 5 mg/day did not increase the incidence of vasomotor symptoms. Simple hyperplasia was noted in 28% of the women. This study therefore suggested that a dose of mifepristone as low as 5 mg/day may be efficacious for the treatment of uterine fibroids, with few side-effects.⁸⁷ The same group of researchers then followed up their preliminary findings with the only published RCT to date on the use of mifepristone for the treatment of uterine fibroids. This was a small study which included 42 women in a double-blind placebo controlled study over a period of 6 months.⁸⁸ They reported that overall quality of life was improved significantly, anaemia rates and uterine volume were reduced significantly, and women were more likely to become amenorrhoeic if they were treated with a low dose of mifepristone.⁸⁸ The hyperplasia seen in some women may limit the use of this drug among those desiring a long-term medical therapeutic alternative. However, the apparent effectiveness of RU 486 in reducing myoma volume, improving fibroid-related symptoms and quality of life, and the minimal side-effects all point to a need for a large RCT with sufficient power to define its true place in the medical management of uterine fibroids. A combination of RU 486 and the LNG-IUS could prove especially useful as the LNG-IUS would obviate the development of endometrial hyperplasia while also promoting a reduction in menstrual flow.

Asoprisnil (selective progesterone receptor modulator)

As with SERMs, and as their name suggests, selective progesterone receptor modulators (SPRMs) have mixed agonist–antagonist activity, and therefore have the potential to exhibit the beneficial effects of progestins and progesterone antagonists, while avoiding their drawbacks. To date, only one SPRM, asoprisnil, has been tested in human clinical trials. Asoprisnil has high tissue selectivity and binds to PRs with a three-fold greater binding affinity than progesterone.⁸⁹ The initial phase I studies established that asoprisnil induced a reversible suppression of menstruation, while having variable effects on ovulation.⁹⁰ The phase 2 multicentre double-blind placebo controlled studies by the same group of researchers compared the efficacy and safety of three doses (5, 10 and 25 mg and placebo) in 129 women over 12 weeks.^{91,92} Asoprisnil reduced the uterine and fibroid volumes in a dose-dependent manner. There was a dose-dependent decrease in menorrhagia scores in women with menorrhagia at baseline, while amenorrhoea rates increased as the dose increased (28.1% with 5 mg, 64.3% with 10 mg and 83.3% with 25 mg), but with no increase in the rates of unscheduled bleeding in all three asoprisnil groups. Bloating was reduced significantly in the 10 mg

and 25 mg groups, and pelvic pressure was reduced significantly in the 25 mg group. Compared with placebo, haemoglobin levels were improved in all three treatment groups, while adverse effects were evenly distributed.

The data available to date on asoprisnil are clearly very encouraging, and its impact on bone mineral density, fertility and recurrence rates of fibroids and endometrial hyperplasia are currently being studied in long-term trials. It is, of course, worth studying the effects of other SPRMs on fibroid disease, and one that is undergoing initial assessment is CDB-2914 (17 α -acetoxy-11 β -[4-N,N-dimethylaminophenyl]-19-norpregna-4,9-diene-3,20-dione).

CABERGOLINE

Most readers will know cabergoline, a lysergic acid derivative, as the dopamine agonist which is widely and effectively used in the treatment of prolactinoma and to inhibit lactation. The theoretical basis for its use in myoma treatment lies in its inhibitory effect (dopaminergic) on the secretion of GnRH. Only one study, from Iran, has compared the effects of GnRHa (diaphereline 3.75 mg every 28 days, total of four injections) with cabergoline (0.5 mg once a week for 6 weeks). This study found significant fibroid regression with both treatments. The extent of tumour regression correlated positively with the number of tumour nodules. Cabergoline was well tolerated and had fewer adverse effects compared with GnRHa.⁹³ Clearly, more studies are required before any definitive conclusions can be made, but this study points to a well-characterized drug as a potentially useful therapy for fibroid disease.

DANAZOL

In gynaecological practice, danazol has probably been used most extensively to treat endometriosis, but due to its side-effects and the advent of newer agents such as GnRHa, its use has declined dramatically over the past decade. Danazol is an isoxazole of 17 β -ethinyl testosterone, a synthetic steroid which is an androgen and a multi-enzyme inhibitor of steroidogenesis, including suppression of oestrogen synthesis. It is also known to suppress sex hormone binding globulin. It has 3% greater affinity for PRs than progesterone and exerts antiprogesterational activity. For these reasons, danazol might be expected to have potential as a therapy for fibroids. Indeed, it has been shown to reduce uterine and myoma volume, and La Marca et al demonstrated a correlation between the reduction in fibroid volume with danazol and an increase in uterine artery impedance, suggesting a vascular effect as a potential mechanism of action.⁹⁴ Compared with gestrinone, danazol induces more rapid endometrial atrophy, with greater impairment of the cytoplasm and cell secretory activity.⁹⁵

Danazol is usually administered at a dose of 100–400 mg/day for 4–6 months. Short-term treatment with danazol results in reduction in mean uterine volume of up to 30% and mean myoma volume of up to 37%. The volume increased at the end of 3 and 6 months after discontinuation of treatment but was still less than the pretreatment volume. Danazol also resulted in an increase in vascular impedance.⁹⁶ Danazol has also been used as an adjuvant therapy after the completion of GnRHa therapy. A study on 21 women who were given danazol 100 mg/day after the completion of six 4-weekly injections of GnRHa showed that there was a reduction in rebound increase in uterine volume. Thus, danazol may be given to prolong the effect

of GnRHa without the problem of menopausal symptoms or bone loss observed with the use of GnRHa for more than 6 months.⁹⁷

However, danazol does have its own significant side-effects. An RCT on the effects of danazol (vs placebo) on endometriosis has reported significant side-effects such as 5% increase in weight gain, pedal oedema, vaginal spotting at 1 and 3 months and not at 6 months, acne etc. However, there was no difference in the side-effects such as muscle cramps, oedema, greasy hair, hot flushes, sweating, decreased breast size, dizziness, decreased libido, nausea, nervousness, hirsutism, headache, insomnia, skin rash and depression.⁹⁸ Lower doses of danazol have been used in the treatment of fibroids (100 mg vs 400 mg in the treatment of endometriosis), with a consequent lower incidence of reported side-effects in this setting.⁹⁶

GESTRINONE

Gestrinone is a tri-enic steroid which exhibits anti-oestrogen and antiprogestosterone activity at the cellular receptor level in the endometrium as well as in other tissue that has ORs and PRs. It also has inhibitory effects on the pituitary, with reversible gonadotrophin inhibition appearing early, from the first month of treatment if it is initiated on the first day of the menstrual cycle. Haemodynamic changes in uterine blood supply have been suggested as another possible mechanism of action.⁹⁹ These properties of gestrinone have been exploited in the treatment of endometriosis, and in its use as a contraceptive agent. Reports on the potential role of gestrinone in the treatment of fibroids emerged in the late 1980s and early 1990s, but all the studies except one originate from one centre, and this agent has not been tested in RCTs against other medications or placebo.

Efficacy in fibroid therapy

In the studies reported, gestrinone was usually given in doses of 2.5–5 mg (orally or by vaginal pessary), two or three times weekly. The vaginal route showed more statistically significant fibroid volume decreases than the oral route for all treatment intervals. Gestrinone has been shown to reduce uterine volume and stop bleeding in observational studies.^{100,101,102} Patients with small tumours, i.e. uterine volumes < 200 cm³, were treated for 6 months, whereas those with uterine volumes of 200–300 cm³ were treated for 1 year. In severe cases where uterine volumes > 400 cm³, the patients were treated for 2 years. Large myomas of 300 cm³ or more required higher doses of steroid.¹⁰⁰ In the observational study using gestrinone for the treatment of large leiomyomatous uteri,¹⁰¹ the mean uterine volume of 724.9 cm³ on admission decreased to 450.73 cm³ at 6 months in all 24 patients treated. In 14 patients treated for a full year, the mean uterine volume of 689.73 cm³ decreased to 329.22 cm³. During the first 6 months of treatment, there was a marked reduction in uterine volume, but subsequently the rate of tumour regression was slower. Suppression of menstruation and alleviation of symptoms such as pelvic discomfort and dysuria were noted in all patients by the end of the second month of treatment. Episodic bleeding occurred in six patients, but this lasted for longer than 1 week in only one patient.

Following discontinuation of treatment, re-activation of tumour growth was slow in most patients. Among patients who discontinued treatment at 6 months, uterine volume remained lower than pretreatment values in 89% of cases at 18 months after discontinuation. Of those patients who discontinued at 1 year, uterine volume remained below pretreatment levels in 76% of cases at 1 year after discontinuation.

In patients treated continuously for 24 months, mean uterine volume decreased significantly from a mean of 339 cm³ to 273 cm³.¹⁰²

Side-effects

Most patients experienced at least some side-effects associated with the mild androgenicity of gestrinone, including weight gain, seborrhoea and acne. Hirsutism, hoarseness and increase in libido were less common, affecting 10–20% of patients depending on the dose and duration of treatment.^{100,101}

NON-HORMONAL THERAPY

Laboratory studies of non-hormonal agents are underway, and focus on identifying compounds that inhibit the actions of specific growth factors. As knowledge of fibroid biology increases, so too does the number of potential therapeutic agents. Thus, some compounds are targeted at inhibiting the proliferation of fibroid cells, decreasing the production of growth factors by fibroid cells, or disrupting collagen synthesis, while others are intended to increase programmed cell death (apoptosis). A variety of substances are undergoing evaluation including antifibrotic agents such as pirfenidone and halofuginone, heparin, interferon- α (IFN- α), thiazolidinediones and tocopherol analogues.¹⁰³ IFN- α , an anti-angiogenic cytokine, is a potent inhibitor of uterine cell proliferation for fibroid, myometrial and endometrial stromal cells in culture.¹⁰⁴ The presence of heparin-binding growth factors suggests a possible focus for therapeutic agents such as heparin and heparin-like agents. Heparin inhibits the motility and proliferation of human myometrial and leiomyoma smooth muscle cells in vitro.¹⁰⁵ RG13577 (a heparin-like compound) and halofuginone (an alkaloid) reversibly inhibit DNA synthesis of normal myometrial and leiomyoma cells without toxic effects.¹⁰⁶ Pirfenidone, a known antifibrotic drug, inhibits DNA synthesis and synthesis of collagen type I mRNA in normal and myoma cells, and only decreases collagen type III mRNA in normal myometrial cells. Pioglitazone, a peroxisome proliferation-activated receptor- γ ligand, is commonly used in the treatment of diabetes mellitus. Pioglitazone significantly inhibits the cell proliferation of both myometrial and leiomyoma cells in a dose-dependent manner.¹⁰⁷

It would therefore appear that the scope for non-hormonal therapies is wide; the challenge is identifying agents that exhibit specificity for myoma cells and have high efficacy with minimal side-effects.

CONCLUSION

It is remarkable that for the most common, albeit benign, tumour of women of reproductive age, there is no effective medical therapy to date. GnRH α (with or without add-back therapy) have a major role to play in gynaecology in general¹⁰⁸ (Table I), and in fibroid disease they are useful pre-operatively. However, the rebound fibroid growth on cessation of therapy, and their significant side-effects and cost, mean that they cannot be used as stand-alone treatments. Aromatase inhibitors and SERMs may be useful in the occasional postmenopausal woman with symptomatic fibroids, but appear to have no beneficial effects in women who need the treatment most, i.e. premenopausal women. The drugs currently showing most promise are arguably the antiprogestogens mifepristone and anisoprisnil. However, they await rigorous evaluation. Non-hormonal therapies are being studied, encouraged by increasing understanding of fibroid biology.

Practice points

- GnRHa are effective in improving haemoglobin concentration and haematocrit, and reducing uterine and fibroid volume, and it has therefore been suggested that they have an important role to play pre-hysterectomy or pre-myomectomy, when it has been shown that they reduce the rate of vertical incisions during laparotomy and increase the rate of vaginal vs abdominal hysterectomy
- Despite the reported benefits above, GnRHa also have disadvantages. They cause bone loss and menopausal symptoms, although both can be alleviated by the use of add-back therapy without interfering with the efficacy of GnRHa. However, the use of GnRHa has not been shown to be cost-effective, and some surgeons argue that they destroy tissue planes and render fibroid enucleation at myomectomy more difficult. In addition, smaller fibroids may be overlooked at the time of surgery, only to recur once GnRHa is discontinued (thereby increasing the apparent risk or recurrence of fibroids following myomectomy). GnRHa cannot be used as long-term stand-alone therapies for fibroid disease because of the rebound growth of the fibroids upon cessation of therapy
- SERMs and aromatase inhibitors are not effective in inducing fibroid regression in the premenopausal women who form the vast majority of patients with fibroid disease. They may have a role to play in the occasional postmenopausal woman with symptomatic fibroids
- There is some evidence that the antiprogestosterone agents mifepristone and asoprisnil may be effective in the treatment of fibroids with respect to improvement in quality of life and reduction in uterine/fibroid volume and symptoms. RCTs of sufficient rigour are awaited
- Medical therapies that may have therapeutic potential, but still require further evaluation, include gestrinone and danazol

Research agenda

- Low-dose mifepristone is a relatively cheap drug with minimal side-effects. A randomized study has suggested that it could be efficacious in reducing fibroid/uterine volume, reducing anaemia rates and improving quality of life. It is imperative that this drug and related molecules (especially asoprisnil) are studied further within the context of rigorously designed RCTs with appropriate power and over sufficiently long periods of time
- The LNG-IUS deserves systematic evaluation as it has already been shown to be efficacious in the treatment of women with menorrhagia but no fibroids. At present, there are suggestions that the presence of fibroids increases the risk of expulsion of the device, but no RCTs have been undertaken, and it is unclear whether expulsion rates are still high when there are no sub-mucous fibroids. A combination of mifepristone and the LNG-IUS could have particular advantages and warrants exploration, as long-term use might be feasible

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