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POSITION STATEMENT

A new approach in the Italian landscape of chronic pelvic pain and endometriosis

New medical approach for treatment of endometriosis

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ABSTRACT

Endometriosis entails a huge burden: it is estimated that affects 10% of women in their reproductive age. Symptoms may be severe (chronic pelvic pain, dysmenorrhea, dyspareunia, dysuria, dyschezia and fatigue) affecting women's quality of life from a personal, familiar, social and professional point of view. Endometriosis may also affect fertility. The economic burden of

endometriosis is relevant. Despite the recent improvements patients 'journey before diagnosis is still long and difficult.

Different options for the treatment have been proposed: hormonal therapies that suppress ovulation and menstruation, surgical treatment or a combination of both.

The most recent tools for the medical management of endometriosis are the oral GnRH antagonists with add-back therapy (ABT). Relugolix Combination Therapy (CT) (40mg Relugolix + 1mgoestradiol as hemihydrate + 0.5mg norethisterone acetate), one tablet daily, is licensed in adult women of reproductive age for symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis as well as for treatment of moderate to severe symptoms of uterine fibroids. The triple combination has the aim of combining the activity on endometriosis's symptoms with the maintenance of oestradiol and progesterone levels in an optimal therapeutic range, in order to minimize the adverse effects.

Nowadays oral relugolix CT may help to solve an unmet need for a condition with such a severe impact on all aspects of women's lives with an effective, well-tolerated, and convenient medical treatment for endometriosis, maintaining a long-term care on women's health, preserving their bone mass.

Key words

Endometriosis; medical therapy; drug combination; GnRH antagonists; relugolix.

Introduction

Endometriosis is a very treacherous issue; even the history of the disease is matter of debate. Officially the disease was identified by von Rokitansky[1]in 1860, but about two centuries before Daniel Shroen had described peritoneal ulcers that tended to form lesions and were susceptible to hemorrhage in women in reproductive age [2]. In our opinion the most interesting description was provided by a Scottish physician, Louis Brotherson, in 1776: he talked about the chronic pelvic pain experienced by women. He also added that "*in its worst stages, this disease affects the well-being of the female patient totally and adversely, her whole spirit is broken, and yet she lives in fear of still more symptoms*"[3].

A cornerstone in endometriosis knowledge is that it is a polygenically inherited disease with a complex, multifactorial etiology[4]. Several theories have been suggested to explain the development of endometrial glands and stroma within the pelvic peritoneum and other extrauterinesites, but the most intriguing aspect of endometriosis pathogenesis is that is a hormone-driven disease [5], dependent on estrogen[6], similar to that seen in eutopicendometrium, but with a lack of consistent response to progesterone or synthetic progestins[7].

Current scenario – The burden of disease

It is estimated that endometriosis affects 10% of women in their reproductive age[8]. In Italy a recent publication using national-level hospital data estimated endometriosis incidence in 0.839 per 1000 women (CI95% 0.834–0.844), while the prevalence rate stood at 14.0 per 1000[9]. It has to be considered that this study only took into account cases intercepted by hospital admissions with a diagnosis of endometriosis(ICD-9-CM, codes 617.x), supported by the presence of a procedure code of laparoscopy or any other surgical procedure allowing for direct visualisation of the lesions; conversely according to other studies [10]it can be speculated that only one-third of women with endometriosis reach a confirmed diagnosis. Therefore, in Italy, there would be more than 500,000 women with endometriosis [9]affected by chronic pelvic pain, dysmenorrhea, dyspareunia, dysuria, dyschezia and fatigue. According to the Ministry of Health the number of women with endometriosis would be 3,000,000 [11]. Endometriosis may also affect fertility by tampering the peritoneal environment or by deforming the pelvic anatomy; about 30% of patients with endometriosis have difficulty conceiving[12].

In Italy around 300,000 women with moderate or severe endometriosis (III or IV degree according to r-ASRM [13])have the right to benefit from certain healthcare services free of charge[14].The exemption is granted during a gynecological examination at a public centre specialized in endometriosis and then submitted by the woman to the Local Health Unit[14].

Endometriosis is associated with a high burden of comorbidities[15], endometriosis-associated pelvic pain is combined with reduced HRQoL, including impaired mental and sexual functioning, as well as reduced work performance and productivity social relationships[16].

The economic burden of endometriosis should not be underestimated, both individually and for the community, as this pathology leads to a loss of productivity at work and large utilization of healthcare resources and personnel costs [15–17].

Despite the recent improvements, due to increased awareness of women and training involvement for healthcare professionals, patients 'journey before diagnosis is long and difficult [15].. It is estimated a delay up to 10-years before diagnosis after the onset of symptoms [15, 18].

More and more scientific evidence is accumulating on the importance of an early diagnosis of endometriosis to limit the psychophysical damage for women[18–20]and the risk of chronic pain development [21]; it has been demonstrated that the efficacy of endometriosis therapeutical approaches due to lack of confidence in the medical profession and in treatment are inversely related to duration of untreated endometriosis [20].

Current scenario – Surgical and medical approaches

Different options for the treatment of patients with symptomatic endometriosis have been proposed: hormonal therapies that suppress ovulation and menstruation, surgical treatment or a combination of both. The management of the disease is driven by symptoms, individual risk factors and informed patient preferences. Nonsteroidal anti-inflammatory drugs may be a helpful first-line treatment for symptoms of dysmenorrhea, but no evidence suggests that they improve non menstrual symptoms[22].

Pharmacologic management of endometriosis includes therapies to decrease endogenous oestrogen, on the basis that oestradiol is a key driver of endometrial growth and local inflammation and pain [23, 24].

Hormonal contraception and progestins are strongly recommended in women suffering from endometriosis-associated symptoms [25]but few drugs are approved specifically for management of pain associated with endometriosis[26]and reimbursed by Italian National Health Services [27].

Oral contraceptives, either administered with a cycle or continuous schedule, or dienogest, a fourth-generation progestin, are generally considered as first-option medical treatment for endometriosis associated with pain symptoms or for preventing postoperative recurrences[25, 28, 29].

Gonadotropin-releasing hormone (GnRH) agonist therapy provides a profound oestradiol suppression, but due to its hypoestrogenic side effects, mainly the diminished bone density ,the duration of use is limited and should require additional concomitant hormonal administration[24, 25, 30].

Surgical treatment is an option when drug therapies are contraindicated (such as for patients who are trying to conceive), are not tolerated or have failed to provide adequate relief or as for patient's choice. A minimally invasive approach with complete treatment of the disease is considered best practice by most international guidelines [25, 31, 32]. Surgical approach is mandatory when endometriosis has conducted to obstructions at ureteric or bowel level. Systematic reviews have shown a persistence or recurrence rate of 22% at 2 years and of 40%–50% at 5 years after surgery[24, 33].

New pharmacological approaches

The most recent tools for the medical management of endometriosis are the oral GnRH antagonists with add-back therapy (ABT). The efficacy is based on the fast binding to the GnRH receptor, blocking endogenous GnRH activity with suppression of LH and FSH production[34]avoiding the flare-up effects observed with GnRH agonists[35, 36].Considering the need of a long-term use, theABT with oestrogen/progestin is an unmissable issue acting as prevention of the side effects of hypoestrogenism (mainly bone loss).

Even if estrogens are considered the primary driver of lesion development, with the loss of progesterone signaling in these tissues [37], however, it is well known that there is a hierarchy of organ response to oestradiol[38]. The current medical position is to consider as not necessary to raze to the ground the oestrogenic concentrations to treat in the long-term women with endometriosis, in order not to expose them to all the dangerous consequences of a prolonged oestrogen deficiency. The goal is to maintain the oestradiol concentrations in the range of 30-45pg/ml, instead. This is the right threshold that does not stimulate endometriotic lesion to growth, and in the meantime, it can avoid the short and long-term consequences, mainly on osteocalcium metabolism and bone structure, badly affected by a profound hypoestrogenism [39]. The bone health is a major health objective since 1998, when the European Commission report on

osteoporosis was published with the objective to reach a significant reduction in the incidence of osteoporosis and related fractures [40]. The burden of osteoporosis for Italian women is huge, considering the epidemiological figures and the scarce awareness among patients (only one in two women knows she is affected) and healthcare professionals[41].

Relugolix Combination Therapy (CT) (40mg Relugolix + 1mgoestradiol as hemihydrate + 0.5mg norethisterone acetate), one tablet daily, is licensed in adult women of reproductive age for symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis as well as for treatment of moderate to severe symptoms of uterine fibroids [42].

The pharmacodynamic properties of the combination are the following:

1. Relugolixis a phenylurea derivative, with an affinity 52 times higher for GnRH receptor in the anterior pituitary than endogenous GnRH; it has the aim of decreasing oestrogen and progesterone production [43, 44].
2. oestradiol maintained at concentrations consistent to those detectable in the early follicular phase of the menstrual cycle; it has the aim of preserving bone mineral density and significantly improving the patient's quality of life[45, 46]. In the phase 3 clinical studies, in patients with endometriosis oestradiol concentrations were approximately 38 pg/mL, corresponding to oestradiol concentrations in the early follicular phase of the menstrual cycle[42], thus completely within the oestrogen therapeutic window stated by the oestrogen threshold hypothesis [39].
3. norethisterone acetate a synthetic progestin; it has the aim of reducing the risk of oestrogen-induced endometrial hyperplasia[42]. Furthermore, the action this progestin on bone density is well documented [47–49].

In the phase 3 double-blind trials (SPIRIT 1 &SPIRIT 2), involving nearly 1.300 women with confirmed endometriosis, a higher proportion of the sample met the dysmenorrhea responder criteria and the non-menstrual pelvic pain responder criteria in the Relugolix CTgroup compared to placebo group(Figure 1)with a similar incidence of adverse events. The evaluation of time to response indicates benefit as early as 4 weeks after starting treatment with maximum effect at 8

weeks for dysmenorrhoea and 12 weeks for non-menstrual pelvic pain. The endometriosis Health Profile-30 pain domain, mirroring the effects of pain on daily function, improved significantly in the Relugolix CT group compared with placebo. Lastly, more women in the Relugolix CT group were opioid free at week 24 compared to the placebo group.

In addition, RelugolixCT is able to provide inhibition of ovulation in women taking the recommended dose and provides adequate contraception after at least one month of use, but the median time of menses return was 31 days(IQR 21–36) after stopping treatment for the RelugolixCT[50].

Within a single cohort study, the return of ovulation after discontinuation of treatment occurred within 43 days (mean 23.5 days) in the whole sample of healthy premenopausal women participating in the study[42].

In the SPIRIT open-label extension study the proportion of responders at Week 104/End of treatment was 84.8% for dysmenorrhea and 75.8% for non-menstrual pelvic pain; both decreases in dyspareunia and improvement in EHP-30 pain domain were also sustained for the whole period. Eventually, at Week 104/End of treatment75% of patients were analgesic-free and 91% were opioid-free. After initial least squares mean BMD loss <1% at Week 24, at Week 36 a BMD plateau was evident and was sustained up to 104 weeks of treatment[26](Figure2).

Conclusions

Endometriosis is a widely diffused condition; in most cases patients' journey to receive diagnosis and treatment is troublesome and exhausting. Endometriosis may cause considerable distress and can heavily affect women's lives, potentially leading to the development of chronic pelvic pain, infertility or end-organ damage. Therefore, early recognition and diagnosis are crucial to providing timely treatment: all healthcare professionals in contact with women should enhance their ability to make a prompt clinical diagnosis of endometriosis and engage their patients in the correct disease' management.

Nowadays oral relugolix CT may help to solve an unmet need for an effective, well-tolerated, and convenient medical treatment for endometriosis, maintaining a long-term care on women's health,

preserving their bone mass. Thereby new efforts from our community are required to identify and tackle a condition with such a severe impact on all aspects of women's lives.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contributions

All authors contributed to the conceptualization, methodology, writing of the original draft, writing, review and editing, and have read and agreed to the published version of the manuscript.

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None of the authors have any conflicts of interest for the present manuscript.

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Informed consent

Not applicable.

Data sharing

Not applicable.

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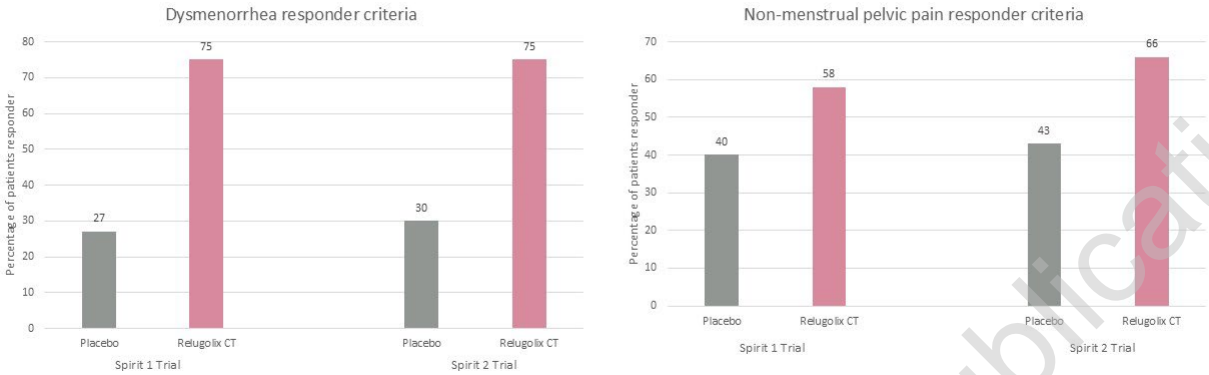
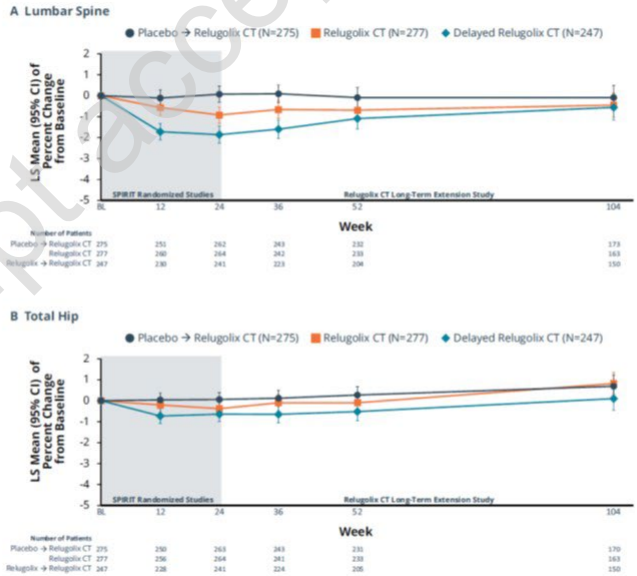
Figure 1.
Clinical trials: reduction in pain symptoms



Results of the registrative trials of Relugolix-CT Spirit 1 and Spirit 2.
Proportion of patients who respondedto treatment (%) for dysmenorrhoea and non-menstrual pelvic pain in Spirit 1 and Spirit 2 at week 24. The responder rates are both based on Numerical Rating Scores NRS and analgesic use
(Modified from Giudice, LC et al.*"Once daily oral relugolix combination therapy versus placebo in patients with endometriosis-associated pain: two replicate phase 3, randomised, double-blind, studies (SPIRIT 1 and 2)."* Lancet (London, England) vol. 399,10343 (2022): 2267-2279. doi:10.1016/S0140-6736(22)00622-5)

Figure 2.
Clinical trials: impact on BMD



Percentage change from baseline in bone mineral density over time for lumbar spine and total hip. During the first 24 weeks of treatment,
patients receive one of three randomized treatments: relugolix CT (combination therapy), relugolix for 12 weeks +relugolix CT for 12 weeks, or placebo. At Week 24, with the beginning of the SPIRT long-term extension study, all patients received relugolix CT.

(A) Data for lumbar spine.(B) Data for hip.
Becker, Christian M et al. *“Two-year efficacy and safety of relugolix combination therapy in women with endometriosis-associated pain: SPIRIT open-label extension study.”* Human reproduction (Oxford, England) vol. 39,3 (2024): 526-537. doi:10.1093/humrep/dead263