At last, an orally active gonadotropin-releasing hormone antagonist

In July 2018 the U.S. Food and Drug Administration (FDA) approved, for the first time, an orally active gonadotropin-releasing hormone (GnRH) antagonist. My first thought was, I only wish that Gary Hodgen had lived long enough to see this day. I remember listening to his wonderfully prescient lectures on GnRH and its analogs in the early 1990s, dreaming of all that was going to be possible when the GnRH antagonists finally became a reality (1). Gary was a brilliant researcher and spent many years performing pioneering studies on prototypes of GnRH antagonists, which promised to transform reproductive medicine.

The tacit assumption, of course, was that the antagonists, like the agonists, were going to have a peptide structure similar to native GnRH and thus would have to be administered by injection. Nevertheless, their ability to acutely, and reversibly, suppress gonadotropin secretion seemed nothing short of magical. This was what I was looking forward to. It did not occur to me that it might be possible to synthesize a nonpeptide molecule that would nevertheless sufficiently resemble a peptide that it could be used to competitively antagonize a protein hormone—and yet be administered orally. Having witnessed the evolution of the GnRH antagonists, I cannot help but feel that this is game changer.

The discovery of the structure of GnRH in 1972 was the culmination of a race between two investigators, Andrew Schally and Roger Guillemin, who went on to share the 1977 Nobel Prize for its discovery (2, 3). The importance of this discovery was immediately apparent because control of the receptor of GnRH would permit modulation of the reproductive function. The structure of GnRH turned out to be that of a decapeptide with a very short half-life (2 to 4 minutes). Early attempts at producing analogs of GnRH focused on substituting some of the amino acid residues to prevent its rapid degradation and thus increase its half-life. The part of the GnRH molecule that bound the receptor was left alone. This is how GnRH agonists were produced. However, the pituitary response to GnRH turned out to be highly dependent on its pulsatile secretion. Whereas hourly pulses of GnRH could induce ovulatory menstrual cycles in primates (4), continuous stimulation of the receptor led to diminishing luteinizing hormone and follicle-stimulating hormone secretion. Thus, the agonists, with much longer half-lives than native GnRH, produced only a temporary increase in gonadotropin secretion followed by suppression.

Clinical applications of the agonists are now well known. With the exception of the "flare" protocol for controlled ovarian stimulation, GnRH agonists are used for their suppressive properties. The initial agonistic response gives way to suppression within 7 to 10 days after administration is begun. The suppression is predictable and reversible, and it can be sustained indefinitely for as long as the medication is administered. The development of depot formulations has obviated the need for daily parenteral administration via injections or nasal inhalants.

We use GnRH agonists for a variety of estrogen-dependent diseases, including endometriosis, fibroids, abnormal uterine bleeding, polycystic ovary syndrome, precocious puberty, estrogen-dependent malignancies, and as adjuncts to ovarian stimulation for in vitro fertilization (IVF). In men, they are analogously used for suppression of testosterone-dependent diseases. The only "clumsy" aspect of their administration is the imprecise and inconvenient nature of the initial agonistic phase, which requires a delay in the onset of the gonadal suppression and which may temporarily exacerbate the condition being treated. This is where the GnRH antagonists have a clear advantage.

The development of a clinically useful GnRH antagonist proved far more challenging than the synthesis of agonists. The structure of native GnRH had to be modified not simply to change its half-life but also in the receptor-binding region so that the resulting molecule would bind the receptor and yet not cause activation and subsequent gonadotropin secretion. Early antagonists were associated with histamine release, which limited their clinical utility. Several generations of antagonists were synthesized and studied before ganirelix and cetrorelix were eventually developed and approved for adjunctive use in controlled ovarian stimulation. They produce an immediate suppression of gonadotropin secretion, and their utility has led to their wide use in IVF stimulation protocols. What the injectable antagonists have not done is to replace long-term GnRH agonist treatment for suppression of estrogen-sensitive diseases such as endometriosis. For these therapeutic purposes, the depot formulation of a GnRH agonist remains the most convenient. However, this may well change as some patients will likely prefer a daily oral dose of an antagonist.

The therapeutic potential of orally active antagonists of GnRH cannot be overstated. They have none of the inconvenience of injectable medications. They can rapidly and reversibly suppress pituitary gonadotropin secretion, and their dose can be titrated to the desired degree of suppression. In addition to replacing GnRH agonists for suppression of estrogen-dependent diseases, they may well provide an attractive alternative to oral contraceptives, for both contraceptive and noncontraceptive purposes.

Because ovulation can be blocked acutely, the antagonists can be used for standard as well as postcoital contraception. They can be used by women who cannot tolerate synthetic steroid hormones. Male contraception with a combination of a GnRH antagonist and testosterone add-back may at last become a reality. Arguably, all noncontraceptive uses of oral contraceptives may be replaced by the orally active GnRH antagonists. The list is virtually endless: scheduling ART cycles, temporary therapy of menorrhagia, dysmenorrhea, prevention of ovulation before gynecologic procedures, control of endometrial thickness before hysteroscopy, or treatment of endometrial hyperplasia.

I remember hearing about these potential applications more than 25 years ago in Gary Hodgen's lectures and articles (5). I believe that we are at last standing on the threshold of a new explosion of clinical studies. When one considers the

path from the discovery of GnRH to the development of its agonists and antagonists, this most recent step, the development of an orally active antagonist, represents the culmination of decades of work. It is definitely a game changer. I only wish that Gary had lived long enough to see this day.

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REFERENCES

1. Gordon K, Hodgen GD. Basis for differential therapeutic roles of GnRH agonists versus antagonists in clinical practice. Infertil Reprod Med Clin North Am 1993;4:201–13.
2. Matsuo H, Baba Y, Nair RM, Arimura A, Schally AV. Classic pages in obstetrics and gynecology. Structure of the porcine LH-and FSH-releasing hormone. I. The proposed amino acid sequence. Biochem Biophysical Res Commun 1971;43:1334–9, Am J Obstet Gynecol 1976;125:1141.
3. Burgus R, Butcher M, Amoss M, Ling N, Monahan M, Rivier J, et al. Primary structure of the ovine hypothalamic luteinizing hormone-releasing factor (LRF). Proc Natl Acad Sci USA 1972;69:278–82.
4. Belchetz PE, Plant TM, Nakai Y, Keogh EJ, Knobil E. Hypophysial responses to continuous and intermittent delivery of hypothalamic gonadotropin-releasing hormone. Science 1978;202:631–3.
5. Gordon K, Hdgen GD. Will GnRH antagonists be worth the wait? Reprod Med Rev 1992;1:189–94.