Reproductive BioMedicine Online (2014) 28, 183–190

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REVIEW

Ovarian response markers lead to appropriate and effective use of corifollitropin alpha in assisted reproduction

Antonio La Marca *, Giovanni D'Ippolito

Mother-Infant Department, Institute of Obstetrics and Gynecology, University of Modena and Reggio Emilia, 41100 Modena, Italy
* Corresponding author. *E-mail address:* antlamarca@libero.it (A La Marca).

Antonio La Marca is a professor for reproductive medicine at the Mother-Infant Department, University of Modena and Reggio Emilia, Modena, Italy. He trained at the University of Siena, where he graduated in medicine in 1996 and completed his residency in obstetrics and gynaecology in 2001. His PhD was on biology of germ cells. Since 2004, he has worked at the unit for reproductive medicine and surgery of the University Hospital of Modena. His research areas are the physiology of ovarian function and its pharmacological manipulation. In the last years, his research has been focused particularly on anti-Müllerian hormone, antral follicle count and ovarian reserve.

Abstract Corifollitropin alpha is a highly effective gonadotrophin, which maintains multifollicular growth for a week. The advantages of its administration include ease of use of the drug, making the treatment more patient friendly, resulting in a lower level of distress for the patient. At the same time, the pregnancy rate resulting from its use in IVF/intracytoplasmic sperm injection cycles is similar to that found when daily recombinant FSH is administered. The ovarian response to corifollitropin alpha is dependent on clinically established predictors such as baseline FSH, antral follicle count (AFC) and age. There is a general trend towards a higher ovarian response with an increasing AFC and the number of oocytes per attempt decreased with increasing baseline FSH and age. Even if the risk of ovarian hyperstimulation syndrome following corifollitropin alpha is very similar to the rate reported in literature for young women undergoing IVF, the risk of overstimulation may be reduced by avoiding maximal ovarian stimulation in women anticipated to be hyperresponders. High basal anti-Müllerian hormone and/or AFC can identify women with enhanced functional ovarian reserve at risk of overstimulation, and the risk is even higher if maximally stimulated with corifollitropin alpha or high dose of daily recombinant FSH.

KEYWORDS: antral follicle count, anti-Müllerian hormone, corifollitropin alpha, IVF, OHSS, ovarian stimulation

Introduction

Many infertility treatment protocols have been proposed over the last decades, but all of them consisted in daily injection of gonadotrophins in combination with gonadotrophin-releasing hormone (GnRH) analogues. In recent years, many therapeutic areas shifted from more complex drug delivery regimens, for example with daily injections, to drugs that require reduced frequency of administration. Many are the advantages from such kind of

1472-6483/$ - see front matter
http://dx.doi.org/10.1016/j.rbmo.2013.10.012

administration including the easy use of the long-acting drugs which makes the treatment more patient friendly and gives lower level of distress to the patient. Another advantage is that fewer injections may improve drug compliance and, as in IVF treatment, prevent errors during gonadotrophin administration, which are very common (Fauser et al., 2009; Verberg et al., 2008).

Corifollitropin alpha is a new sustained recombinant gonadotrophin able to promote and to maintain multifollicular growth throughout the first 7 days of ovarian stimulation. The pharmacokinetic profile of corifollitropin alpha is characterized by a slow absorption after subcutaneous absorption, resulting in peak concentrations 2 days after injection with a steady decline afterwards. Its very long elimination half-life leads to serum FSH concentrations above the threshold window, hence efficiently supporting ovarian stimulation over an entire week (Fauser et al., 2010). This sustained activity may be perceived by many clinicians as it could increase the risk for overstimulation in some patients undergoing IVF.

The objective of this article is to summarize the most relevant pharmacological characteristics of this drug and suggest how to use markers predicting ovarian response in order to guide an appropriate drug prescription in the clinical practice.

From daily to once-a-week FSH injection

In the 1990s, the more common used gonadotrophins to induce ovulation were the human menopausal gonadotrophins that have FSH and LH activity, while the first recombinant FSH preparation became commercially available in 1996 (De Leeuw et al., 1996; Howles, 1996; Olijve et al., 1996). Recombinant FSH has a relatively short half-life and requires daily injections in order to maintain the serum FSH concentration beyond the threshold useful for the production of ovarian stimulation. Recombinant FSH has a $t_{1/2}$ of about 30 h and after each injection the peak FSH serum concentrations are reached in 10–12 h. Steady-state concentrations are reached after 3–5 days. Of course, all of these pharmacodynamic and pharmacokinetic properties are influenced by individual characteristics such as gender and weight, but also by route of administration (Fauser et al., 2010; le Cotonnec et al., 1998).

Structure analyses of gonadotrophins revealed the importance of O-linked and N-linked glycosylation sites and their impact on the prolongation of hormone half-life (Loumaye et al., 1996; Porchet et al., 1994; Quinton et al., 1996). For instance, the human chorionic gonadotrophin (HCG) C-terminal region, which has four serine O-linked oligosaccaride chains, was absent in the other glycoprotein gonadotrophin hormones and was thought to be responsible for the prolonged half-life and the slower metabolic clearance compared with LH. As a matter of fact, the deletion of the C-terminal peptide (CTP) of the HCG β-subunit resulted in a derivative that was 3-fold less active than the native HCG, confirming the importance of this small peptide. In order to reduce the frequency of injections necessary during ovarian stimulation for IVF, long-acting FSH molecules have been developed. One sustained FSH preparation was recently developed and called corifollitropin alpha. Professor Irving Boime at Washington University developed the CTP technology on which corifollitropin alpha was based in the 1990s. Corifollitropin alpha consists of a α-subunit identical to that FSH and a β-subunit produced by fusing the CTP of the β-subunit of HCG with the β-subunit of FSH. (Fares et al., 1992; LaPolt et al., 1992). The advantage of this preparation is that corifollitropin alpha interacts only with the FSH-receptor and lacks LH activity (Fauser et al., 2009; LaPolt et al., 1992; Loutradis et al., 2010), but it has a longer half-life and an extended time-interval to peak serum concentrations than recombinant FSH. After a single corifollitropin alpha injection, the time to reach the serum peak concentrations is about 44 h and its elimination half-life is approximately 69 h (Corifollitropin Alfa Dose-finding Study Group, 2008).

Once it was proven that the corifollitropin alpha's half-life is approximately twice as long as that of recombinant FSH (Balen et al., 2004; Bouloux et al., 2001; Duijkers et al., 2002) and that its administration is well tolerated, the aim was to find the right dose to sustain a multifollicular growth during ovarian stimulation within a protocol that entails the daily administration of GnRH antagonist to prevent the LH surge. Devroey et al. (2004), using single doses of 120, 180 or 240 μg in a GnRH antagonist protocol, showed that this range dose was effective to induce and sustain multifollicular growth for 7 days. Four years later, the Corifollitropin Alfa Dose-finding Study Group (2008) designed a phase-II study to investigate the dose–response relationship according to the number of retrieved oocytes. Modelling and simulation techniques were then used to explore the impact on treatment outcome of various doses of corifollitropin alpha as well as the influence of patient characteristics. Bodyweight was a major determinant of exposure to corifollitropin alpha and treatment outcome. It was concluded that the recommended dose of corifollitropin alpha was 150 μg for patients with a bodyweight $>$60 kg and 100 μg for patients with a bodyweight $\leq$60 kg (De Greef et al., 2010).

Corifollitropin alpha is a highly effective ovarian stimulator

The calculated dose of corifollitropin alpha was then tested in the ENGAGE trial (Devroey et al., 2009), including 1509 women with a bodyweight $>$60 kg and in which efficacy and safety of a single injection of 150 μg corifollitropin alpha was compared with the daily injection of 200 IU recombinant FSH. Women included in the study were aged 18–36 years, with a bodyweight of 60–90 kg, regular menstrual cycles, with an antral follicle count (AFC) of less than 20 in both ovaries and a serum day-3 FSH $<$12 IU/l. Hence women treated in the trial may be considered as potential normal responders, since many poor- and hyperresponders were excluded on the basis of AFC and serum FSH. In the corifollitropin alpha group, 33% of the patients (259 of 755) met the criterion for HCG administration before or on stimulation day 8 (Fauser et al., 2010). The remaining women needed some days of daily recombinant FSH injections to reach the above said criterion with a median duration of stimulation of 9 d. On the day of HCG injection, a higher