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Research Article

Corifollitropin Alfa in Poor Responders: Preliminary Results

Leonardo Rinaldi* and Helmie Selman
One Day Medical Center, Italy

***Corresponding author:** L. Rinaldi, One Day Medical Center–IVF Unit, Via Attilio Ambrosini 114, 00144 Roma, Italy

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Abstract

Corifollitropin Alfa is a long acting synthetic recombinant follicle-stimulating hormone (FSH-CTP) molecule which has been recently proposed in poor responder's stimulation protocols.

In a retrospective study, we analyzed 30 patients identified as poor responders' patients according to the Bologna Criteria which underwent ovarian stimulation with clomiphene, corifollitropin Alfa and rFSH. We compare the results with those obtained in a historical control group of 35 patients which underwent ovarian stimulation with clomiphene and rFSH.

No significant differences were observed between the two groups in terms of the mean age (Group A 40.9 ± 2.8 years vs Group B 41.1 ± 3 years), the length of stimulation (Group A 13,3 ± 4.5 days vs Group B 12.4 ± 2.2 days), the number of cancelled cycles (Group A = 5 (16,6%) vs Group B = 5 (14,2%)), the number of retrieved oocytes (Group A 2.6 ± 1.5 vs Group B 2.7 ± 1.5), the number of embryos transferred (Group A 1.7 ± 1 vs Group B 1.9 ± 0.9), and the number of patients with transfer (Group A 24/30 (80%) vs Group B 27/35 (77%)). There were also no statistically significant differences between the two groups regarding pregnancy rate per started cycle (Group A 16.6% vs Group B 14.2%), pregnancy rate per embryo transfer (Group A 20% vs Group B 18,5%) and implantation rate (Group A 9,8% vs Group B 10,4%).

Although the relatively small number of studied patients and the retrospective nature of this study we can conclude that corifollitropin Alfa seems to be as efficient as conventional stimulation protocol to treat poor responder patients.

Key words: Corifollitropin Alfa; Poor responders; Ovarian stimulation; *In vitro* fertilization

Introduction

The success of In-Vitro Fertilization (IVF) treatment depends on adequate follicle's recruitment. Failure to obtain adequate number of follicles following controlled ovarian stimulation is mainly observed in "poor responders" patients [1]. Many treatment protocols targeted to such women have been proposed, and the increase of the number and quality of oocytes recovered in these patients remains one of the most challenging items of assisted reproduction technologies [2].

Corifollitropin Alfa has been recently introduced for controlled ovarian hyper stimulation in general population [3]. It is a long acting synthetic recombinant follicle-stimulating hormone (FSH-CTP) molecule with a specific characterizes, such as long elimination half life and short time to reach its peak serum concentration, that confer its efficacy for ovarian stimulation treatment. Due to its pharmacokinetic profile, it has been recently suggested that corifollitropin Alfa could have a role in poor responders' stimulation protocols [4].

In our study we report on the use of the corifollitropin Alfa to stimulate a group of poor responders' patients, compared to commonly used protocols for the treatment of poor responders' patients in our center.

Material and Method

In a retrospective study, we analyzed 30 patients, with a mean age 40.9 ± 2.8 years, identified as poor responders from October 2012 to July 2013. Poor responders' women were identified according to the recently stated Bologna Criteria [5]. In summary, in order to define the poor response in IVF at least two of the following three features must be present: 1) advanced age (> 40 years) or any other risk factor for poor ovarian response; 2) poor ovarian response (< 3 oocytes with a conventional stimulation protocol); 3) abnormal ovarian reserve test (antral follicle count [AFC] <7 or antimullerian hormone [AMH] <1.1 ng/mL). Two episodes of poor ovarian response after maximal stimulation are sufficient to define a patient as poor responder in the absence of advanced maternal age or abnormal ovarian reserve test.

The patients (Group A, no=30) were underwent the following stimulation protocol: clomiphene citrate 150 mg administered daily from day 2 to day 6 of cycle. A single dose of 150μg corifollitropin Alfa (Elonva, Merck Sharp & Dohme Limited, Italy), was administered on day 2 of the cycle and thereafter 225 IU of recombinant FSH (rFSH, Gonal F, Merk Serono, Italy) were daily administered starting from day 7 of the cycle onward in a GnRH antagonist cycle. Thirty-five patients (Group B) with a mean age 41.1 ± 3 years were analyzed as a control group. They underwent the following stimulation protocol: clomiphene citrate 150 mg daily administered from day 2 to day 5 of the cycle. A dose of 225 IU of rFSH were daily administered starting from day 3 of the cycle onward in a GnRH antagonist

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cycle. In both groups GnRH antagonist was administered when the leading follicle reached 14 mm, and ovulation trigger was induced by the administration of 10.000 IU of hCG. Oocyte retrieval, embryo culture and embryo transfer were carried out in accordance with the usual clinical practice. All available embryos were transferred into the uterus. Primary end points analyzed were: mean age, length of stimulation protocol, number of cancelled cycles number of oocytes recovered, number of cleaving embryos, number of embryos transferred, number of patients with transfer. Secondary end points analyzed were: pregnancy rate per started cycle and pregnancy rate per embryo transfer and implantation rate. Statistical analysis was performed evaluating quantitative variables using the Student's t-test and qualitative variables using the chi-square test or the Fisher exact test. Statistical significance was set at $P \leq 0.05$.

Results and Discussion

No significant differences were observed between the two groups in terms of the mean age (Group A 40.9 ± 2.8 years vs Group B 41.1 ± 3 years), the length of stimulation (Group A 13,3 ± 4.5 days vs Group B 12.4 ± 2.2 days), the number of cancelled cycles (Group A = 5 (16,6%) vs Group B = 5 (14,2%)), the number of retrieved oocytes (Group A 2.6 ± 1.5 vs Group B 2.7 ± 1.5), the number of embryos transferred (Group A 1.7 ± 1 vs Group B 1.9 ± 0.9), and the number of patients with transfer (Group A 24/30 (80%) vs Group B 27/35 (77%)). There were also no statistically significant differences between the two groups regarding pregnancy rate per started cycle (Group A 16.6% vs Group B 14.2%), pregnancy rate per embryo transfer (Group A 20% vs Group B 18,5%) and implantation rate (Group A 9,8% vs Group B 10,4%) (Table I).

The incidence of poor responding patients varies among 9 and 24% according to different studies reported in the literature and is bound to augment with the increasing age of the patients undergoing assisted reproduction technologies [6,7]. In a recent Cochrane review, Pandian et al. [2] analyzing 10 randomized controlled trials concerning different protocols of stimulation used for poor responder patients, they found that there is insufficient evidence to support the routine use of any protocol in the treatment of poor responder women. . Furthermore, the ESHRE working group on Poor Ovarian Response (POR) definition has produced a consensus paper identifying three features of poor ovarian response (Bologna Criteria): (i) advanced maternal age or any other risk factor for POR; (ii) a previous POR; and (iii) an abnormal ovarian reserve test (ORT). The presence of two of these features identifies a poor responding patient.

Moreover two episodes of POR after maximal stimulation are sufficient to define a patient as poor responder in the absence of advanced maternal age or abnormal ORT [5]. In our study we choose to add clomiphene citrate to gonadotropin treatment protocols, because clomiphene is an anti-oestrogen agent which competes with the endogenous oestrogens for receptor binding sites. By blocking receptors in the hypothalamus and pituitary gland, clomiphene interferes with the feedback mechanism of the endogenous oestrogen on the pituitary gland and hypothalamus, resulting in an increase in FSH and LH secretion by the pituitary gland. Of note that the clomiphene-induced elevation of gonadotropin stimulates the production of ovarian follicles (folliculogenesis) and ovulation, and its use has been advocated as beneficial in poor responders patients by some authors [8,9] even though a general agreement is lacking [10].

Table 1: Embryological and clinical outcome.

	Group A Coriofollitropin + rFSH	Group B rFSH	p
N. of patients	30	35	
Mean age±SD	40.9 ± 2.8	41.1 ± 3	NS
N. of cancelled cyles	5 (16.6%)	5 (14.2%)	NS
N. of patients with failed fertilization	1	3	NS
N. of patients with embryo transfer	24	27	NS
Lenght of stimulation (days) ±SD	13.3 ± 4.5	12.4 ± 2.2	NS
N. of recovered oocytes ±SD	2.6 ± 1,5	2.7 ± 1.5	NS
N. of embryos transferred ±SD	1.7 ± 1	1.9 ± 0.9	NS
N. of pregnancies	5	5	NS
Pregnancy rate per embryo transfer%	20%	18.5%	NS
Pregnancy rate per started cycle%	16.6 %	14.2%	NS
Implantation rate%	9.8%	10.4%	NS

NS: Not Significant

In our study we used a long acting gonadotropin in the first part of the stimulation although all preliminary studies on corifollitropin Alfa expressly excluded poor responders [11] from studied population. However, considering the peculiar pharmacokinetic profile of this new gonadotropin, with an approximately two-fold longer elimination half-life and an almost four-fold extended time to peak serum levels when compared with rFSH [12,13], it might have a beneficial effect during the recruitment phase of follicular growth. In fact, corifollitropin Alfa consent the exposure of the small antral follicles to a constant high levels of FSH during the early follicular phase, which is crucial in poor responder patients.

Attempts to study the role of corifollitropin Alfa in poor responder patients have been firstly reported by Polyzos et al in two different retrospective study [14,15]. In the first study, comparing corifollitropin Alfa combined with rFSH in GnRH antagonist protocol to standard HMG in GnRH agonist protocol, the authors did not found any differences between the two groups in all studied parameters. In the second study, the same authors have treated a group of poor responder patients with corifollitropin combined with hp-HMG in a GnRH antagonist protocol. They matched the patients in two groups according to the age: ≤40 years and ≥40 years. No differences were observed between the two groups in terms of endocrine profile, number of cycles with oocyte retrieval and number of cycles with embryo transfer. However, considering ongoing pregnancy rate, the authors observed a statistically significantly higher pregnancy rate in favor of patients aged ≤ 40 years than those ≥ 40 years (28% versus 0% respectively) [15].

Our results, however, show a pregnancy rate 20% in patients treated with corifollitropin even though the mean age of patients was ≥ 40 years. Despite this fact and due to the small number of studied patients we are not able to evaluate the possible different role of corifollitropin Alfa in patients ≤40 years or ≥40 years. Our results also show that no significant differences were observed between corifollitropin group and standard protocol group in terms of all studied parameters including pregnancy and implantation rate.

Conclusion

Although the relatively small number of studied patients and the

retrospective nature of this study we can conclude that corifollitropin Alfa seems to be as efficient as conventional stimulation protocol to treat poor responder patients. Indeed, further prospective randomized studies on large number of patients should be addressed in order to investigate the efficacy of corifollitropin Alfa in treatment of poor responder patients.

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