

Poster #28

FSH treatment improves sperm DNA damage in men with idiopathic infertility carriers of the FSH receptor p.N680S homozygous N genotype: an interim analysis.

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BACKGROUND: Follicle-stimulating hormone (FSH) is fundamental for spermatogenesis and is empirically used to treat male idiopathic infertility. In a subgroup of men FSH treatment causes a significant improvement of the sperm DNA fragmentation (sDF), a candidate predictor of the probability to conceive. However, 40% of men do not show any sDF change during FSH treatment. Since the FSH receptor (FSHR) polymorphisms (SNP) p.N680S clearly influences ovarian response in women and testicular volume in men, this SNP might be useful to predict response to FSH.

AIM: To evaluate whether sDF improvement in response to FSH therapy depends on FSHR p.N680S.

METHODS: A multicenter, longitudinal, prospective, open label, two arms clinical trial is ongoing. So far 61 men with idiopathic male infertility carrier of the homozygous FSHR p.N680S N or S genotype, FSH<8 IU/L and sperm DF>15%, were enrolled and 42 completed the study protocol. All subjects received 150 IU of recombinant FSH (Gonal f®) every other day for 12 weeks and were then followed-up for further 12 weeks after FSH withdrawal. sDF was evaluated by TUNEL/PI assay coupled to flow cytometry, resolving two different sperm population, namely: Plbrighter and Pldimmer. Ultrasound testicular volume and sperm count were assessed at the centers. The centers were blind to the FSHR genotype, which was assessed centrally.

RESULTS: 25 men (59.5%) were carriers of the p.N680S homozygous N and 17 (40.15%) of the homozygous S genotype, respectively. Total sDF (Plbrighter+Pldimmer) was significantly lower at the end of the study in patients carriers of the p.N680S N allele than patients carriers of p.N680S S allele (p=0.017). Only in patients carriers of the p.N680S N allele, total sDF decreased significantly from baseline to the end of the study (p=0.021) and this decrease was entirely sustained by the sperm population containing vital sperms (i.e. the Plbrighter fraction) (p=0.008). On the contrary, the Pldimmer fraction, which includes only non-vital sperms, was significantly higher in patients carriers of the p.N680S S allele than in carriers of N allele (p=0.018). Total sDF was also inversely related to total sperm number (p=0.020) and progressive sperm motility (p=0.014).

CONCLUSIONS: The interim analysis of this ongoing study suggests that a significant improvement of total sDF is achieved in men carriers of the p.N680S homozygous N allele after 12 weeks of FSH treatment. This sDF decrease is explained by the decrease of the Plbrighter fraction, representing the subgroup containing vital and mobile sperms. If confirmed, this study shows that sDF is a good pharmacodynamics parameter of response to FSH treatment in men with the homozygous FSHR p.N680S N allele, paving the way to a pharmacogenetic approach to FSH treatment of male idiopathic infertility. (EudraCT 2010-020240-35)