

## Perspectives and Editorials:

## Letters to the Editor

### **Responsiveness to Tamoxifen Citrate and Testosterone Undecanoate Is Independent of the Severity of Idiopathic Oligozoospermia**

*To the Editor:*

In their recent article, “Cinnocicam and L-Carnitine/Acetyl-L-Carnitine Treatment for Idiopathic and Varicocele-Associated Oligoasthenospermia,” Cavallini et al (*J Androl.* 2004;761–770) made a reference to our recent publication (Adamopoulos et al, 2003), citing this article on 3 occasions, with a fourth citation coming from the ensuing “Editorial Commentary,” by Comhaire and Mahmoud (*J Androl.* 2004;771–772).

In the discussion of their paper, Cavallini et al stated that “A survey of the data of Adamopoulos et al (2003) and Wong et al (2002) indicated that their trial predominantly treated patients with isolated alterations of motility, morphology or both who have normal concentration of sperm.” This was a rather misguided interpretation of our clinical trial and, to put the record straight, we present unpublished details of the study, summarized in Tables 1 and 2.

To begin with, all patients included in our trial (106 men for each of the 2 treatment groups) had sperm concentrations below the 20.0 million spermatozoa per milliliter mark and, as defined by arbitrary World Health Organization (WHO) (1999) criteria, were classified as oligozoospermic. This selection procedure was followed regardless of the total sperm number, which, on certain occasions (placebo, 39.6%; tamoxifen citrate [TMX] + testosterone undecanoate [TU], 27.3%), exceeded that of 40.0 million per ejaculate, the lowest limit proposed by the WHO (1999). In table 1 of our article (Adamopoulos et al, 2003), the mean values for total sperm number were 27.1 (range, 9.4–54.0) and 32.0 (range, 14.1–70.0) million per ejaculate for active and placebo treatments, respectively. At the same time, sperm concentration was 7.9 (range, 3.7–12.1) and 9.1 (range, 3.4–10.9) million per milliliter in the 2 groups. Finally, the means for good motility were  $29.7\% \pm 12.0\%$  and  $29.6\% \pm 15.7\%$ , and

those for conventional normal morphology were  $41.2\% \pm 14.0\%$  and  $45.5\% \pm 16.5\%$  for active and placebo treatment groups.

Moreover, the greatest proportion of men with idiopathic oligozoospermia as defined by their sperm concentration was distributed to the  $1.0$  to  $4.9 \times 10^6/\text{mL}$  (placebo 25.5%; TMX & TU 35.8%) and the  $5.0$  to  $9.9 \times 10^6/\text{mL}$  (placebo 28.3%; TMX & TU 34.9%) subgroups (table 1). A similar, although not quite identical, situation was evident regarding the total sperm number in our clinical material. Therefore, the distribution of our cases in terms of sperm concentration and total number was not skewed toward the upper end of this set of values.

Regarding the response to treatment with TMX and TU, as judged by more than a doubling of the original (basal) sperm concentration and total number, the picture emerged is given in table 2. It is noted that the successful response to treatment was relatively evenly distributed in all sperm concentration subgroups of men treated with this combination, with the exception of the relatively higher first subgroup ( $1.0$ – $4.9 \times 10^6/\text{mL}$ ).

As is obvious from the evidence presented, all the men with idiopathic oligozoospermia included in our study had low sperm concentrations, and most of them had additional aberrations of morphology and motility, but definitely, there were no patients with “isolated alterations of motility, morphology or both who have normal concentrations of sperm,” as stated by Cavallini et al.

This clarification is most important for prescribing practitioners, since Cavallini’s statement may mislead them to exclude from treatment men with very low sperm concentrations who may also have a chance to respond favorably to this treatment, as did patients with higher concentrations in our study. Such an exclusion is most certainly not justified, given the evidence presented. On the contrary, this kind of treatment may be beneficial to the couple since, as has been shown (Comhaire et al, 1995), a sizable improvement in sperm concentration has been linked to disproportionately higher increases in effective cumulative pregnancy rates in men with idiopathic oligozoospermia.

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Table 1. Distribution of cases according to basal 1) sperm concentration and 2) total sperm number

	1) 1.0–4.9*	5.0–9.9	10.0–14.9	15.0–19.9	2) 1.0–19.9**	20.0–39.9	40.0–59.9	60.0–99.9
Placebo treated (%)	27†(25.5)‡	30 (28.3)	28 (26.4)	21 (19.8)	34 (32.1)	29 (27.4)	23 (20.7)	20 (18.9)
TMX + TU§ treated (%)	38 (35.8)	37 (34.9)	25 (23.6)	6 (5.7)	44 (41.5)	33 (31.1)	21 (19.8)	8 (7.3)

\*  $\times 10^6/\text{mL}$ .\*\*  $\times 10^6$ .

† Number of cases (n = 106 per group).

‡ Percentage of total number per group.

§ Tamoxifen citrate plus testosterone undecanoate.

Table 2. Response to therapy according to basal 1) sperm concentration and 2) total sperm count

	1) 1.0–4.9*	5.0–9.9	10.0–14.9	15.0–19.9	2) 1.0–19.9**	20.0–39.9	40.0–59.9	60.0–99.9
Placebo treated (%)	13†(12.3)‡	8 (7.5)	8 (7.5)	1 (0.9)	15 (14.2)	6 (5.7)	2 (1.9)	1 (0.9)
TMX + TU§ treated (%)	22 (20.8)	12 (11.3)	9 (8.5)	7 (6.6)	26 (24.5)	14 (13.2)	5 (4.7)	9 (8.5)

\*  $\times 10^6/\text{mL}$ .\*\*  $\times 10^6$ .

† Number of cases (n = 106 per group).

‡ Percentage of total number per group.

§ Tamoxifen citrate plus testosterone undecanoate.

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## References

- Adamopoulos DA, Pappa A, Billa E, Nicopoulou S, Koukou E, Michopoulos J. Effectiveness of combined tamoxifen citrate and testosterone undecanoate in men with idiopathic oligozoospermia. *Fertil Steril*. 2003;80:914–920.
- Cavallini G, Ferraretti AP, Gianaroli L, Biagiotti G, Vitalli G. Cinnocicam and L-carnitine acetyl-L-carnitine treatment for idiopathic and varicocele-associated oligoasthenospermia. *J Androl*. 2004;25:761–770.
- Comhaire FH, Mahmoud AMA. Editorial commentary. *J Androl*. 2004;25:771–772.
- Comhaire FH, Milingos S, Liapi A, Gordts S, Campo R, Depypere H, Dhont M, Schoonjans F. The effective cumulative pregnancy rate of different modes of treatment of male infertility. *Andrologia*. 1995;27:217–221.
- World Health Organization. *WHO Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interactions*. 4th ed. Cambridge, United Kingdom: Cambridge University Press; 1999.

## Response: Responsiveness to Tamoxifen Citrate and Testosterone Undecanoate Is Independent of the Severity of Idiopathic Oligozoospermia

To the Editor:

I am sorry for the misunderstanding and thank the Editor because he gave me the opportunity to explain the mechanisms that provoked my mistake.

My confusion originates from the following wording: “total sperm count  $\times 10^6/\text{mL}$ ” present in the abstract and in table 1, page 916, of the Adamopoulos article (Adamopoulos et al, 2003). In this regard, I have intended “sperm concentration/ $\text{mL}$ ,” instead of total ejaculated sperm.

The World Health Organization (WHO) handbook does not list any sperm pattern alike: “total sperm count  $\times 10^6/\text{mL}$ ,” and, most importantly, fractional values (ie, . . .  $\times 10^6/\text{mL}$ ) always indicate a concentration (WHO, 1999).

Almost all articles regarding therapy for oligoasthenospermia take into consideration sperm concentration per milliliter instead of total ejaculated sperm (WHO, 1989, 1992; Rege et al, 1997; Kamischke et al, 1998; Rolf et al, 1999; Vicari and Calogero, 2001; Foresta et al, 2002; Wong et al, 2002; Cavallini et al, 2003; Lenzi et al, 2003, 2004; Zawackzi et al, 2003).

It is uncommon to present data regarding number of total ejaculated sperm, even though an increase in sperm concentrations in OAT (oligo-astheno-teratospermia) infertile males has been thought to be associated with disproportionately higher fecundability (Adamopoulos et al, 2003), because the in vivo and in vitro fertilization proved to be more strictly linked to the quality of spermatogenesis than to the number of ejaculated sperm (Tomlinson et al, 1992; Patrizio et al, 1994; Parinaud et al, 1996a,b; Aboulghar et al, 1997; Verheyen et al, 1997; De Croo et al, 2000).

In this regard, sperm concentration per milliliter is more closely linked to the spermatogenic process than to the number of total ejaculated sperm (Biagiotti et al, 2002).

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## References

- Aboulghar MA, Mansour RT, Serour GI, Fahmy I, Kamal A, Tawab NA. Fertilization and pregnancy rates after intracytoplasmic sperm injection using ejaculate semen and surgically retrieved sperm. *Fertil Steril*. 1997;68:108–111.
- Adamopoulos DA, Pappa A, Billa E, Nicopoulou S, Koukoku E, Michopoulos J. Effectiveness of combined tamoxifen citrate and testosterone undecanoate in men with idiopathic oligozoospermia. *Fertil Steril*. 2003;80:914–920.
- Biagiotti G, Cavallini G, Modenini F, Vitali G, Gianaroli L. Spermatogenesis and spectral echo-colour Doppler traces from the main testicular artery. *BJU Int*. 2002;90:903–908.
- Cavallini G, Biagiotti G, Ferraretti AP, Gianaroli L, Vitali G. Medical therapy of oligoasthenospermia associated with left varicocele. *BJU Int*. 2003;91:513–518.
- De Croo I, Van der Elst J, Everaert K, De Sutter P, Dhont M. Fertilization, pregnancy and embryo implantation rate after ICSI in cases of obstructive and nonobstructive azoospermia. *Hum Reprod*. 2000;15:1383–1388.
- Foresta C, Bettella A, Merico M, Garolla A, Ferlin A, Rossato M. Use of recombinant human follicle-stimulating hormone in the treatment of male infertility. *Fertil Steril*. 2002;77:238–244.
- Kamischke A, Behre HM, Bergman M, Simoni M, Schafer T, Nieschlag E. Recombinant human follicle stimulating hormone for treatment of male idiopathic infertility: a randomized double-blind, placebo-controlled, clinical trial. *Hum Reprod*. 1998;13:596–603.
- Lenzi A, Lombardo F, Sgrò P, Salacone P, Caponniecchia L, Dondero F. Use of carnitine therapy in selected cases of male factor infertility: a double blind cross over trial. *Fertil Steril*. 2003;79:292–300.
- Lenzi P, Sgrò P, Salacone P, Paoli D, Gilio B, Lombardo F, Santulli M, Agarwal A, Gandini L. A placebo controlled double blind randomized trial of the use of combined L-carnitine and acetyl-L-carnitine in men with asthenospermia. *Fertil Steril*. 2004;81:1578–1584.
- Parinaud J, Richoille G, Moutaffian H, Vieitez J, Mieusset R. Are the characteristics of spermatozoa in the insemination medium useful for predicting in vitro fertilization results. *Int J Androl*. 1996a;19:103–108.
- Parinaud J, Vieitez J, Moutaffian H, Richoille G, Milhet P. Relationships between sperm motility parameters, morphology and acrosomal reaction of human spermatozoa. *Hum Reprod*. 1996b;11:1240–1243.
- Patrizio P, Ord T, Silber SJ, Asch RH. Correlation between epididymal length and fertilization rate in men with congenital absence of vas deferens. *Fertil Steril*. 1994;61:265–268.
- Rege NN, Date J, Kulkarni V, Prem AR, Puneekar SV, Dahanukar SA. Effect of Y virilin on male infertility. *J Postgrad Med*. 1997;43:64–67.
- Rolf C, Cooper TG, Yeung CH, Nieschlag E. Antioxidant treatment of patients with asthenospermia or moderate oligoasthenospermia with high dose vitamin C and vitamin E: a randomized placebo controlled, double blind study. *Hum Reprod*. 1999;14:1028–1033.
- Tomlinson MJ, Barrat CL, Bolton AE, Lenton EA, Roberts HB, Cooke ID. Round cells and sperm fertilization capacity: the presence of immature germ cells but not seminal leukocytes are associated with reduced success of in vitro fertilization. *Fertil Steril*. 1992;58:1257–1259.
- Verheyen G, Nagy Z, Joris H, De Croo I, Tournaye H, Van Steirteghem A. Quality of frozen thawed testicular sperm and its preclinical use for intracytoplasmic sperm injection into in vitro-matured germinal-vesicle stage oocytes. *Fertil Steril*. 1997;67:74–80.
- Vicari E, Calogero AE. Effects of treatment with carnitines in infertile patients with prostatic-vesiculo-epididymitis. *Hum Reprod*. 2001;16:2338–2342.
- Wong WY, Merkus HM, Thomas CM, Menkveld R, Zielhuis GA, Steegers-Theunissen RP. Effects of folic acid and zinc sulfate on male factor subfertility: a double blind, randomized, placebo controlled trial. *Fertil Steril*. 2002;77:491–498.
- World Health Organization. *WHO Laboratory Manual for the Examination of Human Semen and Semen-Cervical Mucus Interactions*. 4th ed. Cambridge, United Kingdom: Cambridge University Press; 1999.
- World Health Organization Task Force on the diagnosis and treatment of infertility. Mesterolone and idiopathic male infertility: a double blind study. *Int J Androl*. 1989;12:254–264.
- World Health Organization Task Force on the diagnosis and treatment of infertility. A double blind trial of clomiphene citrate for the treatment of idiopathic male infertility. *Int J Androl*. 1992;15:299–397.
- Zawackzi Z, Szollosi J, Kiss SA, Koloszar S, Fejes I, Kowaks L, Pal A. Magnesium orotate supplementation for idiopathic infertile male patients: a randomized placebo controlled clinical pilot study. *Magn Res*. 2003;16:131–136.