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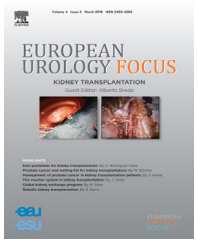

Clinical Trial Update – Andrology

Natesto Effects on Reproductive Hormones and Semen Parameters: Results from an Ongoing Single-center, Investigator-initiated Phase IV Clinical Trial

Thomas Masterson *, *Manuel Molina, Emad Ibrahim, Ranjith Ramasamy*

Department of Urology, University of Miami, Miami, FL, USA

Low testosterone (low T) affects approximately 2–38% of men over the age of 45 yr, with increased prevalence in the elderly [1,2]. Testosterone replacement therapy (TRT) is increasingly becoming available because of increased disease awareness advertising and direct-to-consumer marketing [3]. Current delivery systems of TRT include transdermal gels and patches, injection therapy, and long-acting subcutaneous pellets [4,5]. Unfortunately, TRT cannot be prescribed to men interested in reproduction due to the side effects of decreased sperm concentration and risk of azoospermia [6,7]. Clomiphene citrate, anastrozole, and human chorionic gonadotropin have been used to increase intratesticular T while simultaneously maintaining spermatogenesis. However, they are not without side effects, such as decreased bone mineral density and libido; additionally, they are not Food and Drug Administration (FDA)-approved for treating low T in men [8–10]. Therefore, it is imperative that we identify FDA-approved T therapies that may not affect fertility.

Natesto is a short-acting FDA-approved TRT that is delivered intranasally to men diagnosed with low T. Advantages to intranasal T include ease of delivery, no need for needles, and decreased risk of transference [11]. Recently, Natesto (125 μl/nostril, 11.0 mg T/dose) TID dosing was shown in a multi-institutional study to increase serum T while also maintaining serum levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [12]. We hypothesized that the short half-life of Natesto likely preserves spermatogenesis by maintaining pulsatile release of gonadotropin-releasing hormone, thereby preventing the steep declines in serum LH and FSH routinely seen with other forms of TRT (Fig. 1). Maintaining normal LH and FSH has the theoretical benefit of preserving normal semen parameters while on TRT with Natesto. However, to date, no study has evaluated the effect of Natesto on semen parameters.

We launched our clinical trial to evaluate the role of Natesto on semen parameters and reproductive hormones in November 2017 with the intent of enrolling 40 participants (https://www.clinicaltrials.gov/ct2/show/NCT03203681). It is an ongoing, single-institution, prospective investigator-initiated study funded by Aytu Biosciences. Men eligible for the study are aged 18–55 yr, with at least two T levels <350 ng/dl (drawn before 10 AM) and have two semen analyses (SA) with total motile sperm count (TMSC) >5 million. All men are naïve to T therapy prior to enrolment.

We collected baseline serum T, LH, FSH, two SA, 15-question International Index of Erectile Function Questionnaire (IIEF-Q15) and Short Form Health Survey (SF-36) scores. After consenting, patients were prescribed Natesto 4.5% nasal T. Dosing includes two pumps, one per nostril for a dosing of 11 mg, three times a day (33 mg delivery daily) as described on the label. Serum reproductive hormones, SA, and questionnaires will be collected at 3 and 6 mo of therapy. The duration of this study is 6 mo.

To date, we have enrolled 23 men. Their median age is 35 (interquartile range: 31.7–37.8) yr with baseline T 228.8

* Corresponding author. Department of Urology, University of Miami, 1120 NW 14th Street, Miami, FL 33136, USA. Tel. +1 305 243 4562.
E-mail address: ranjithrama@gmail.com (T. Masterson).

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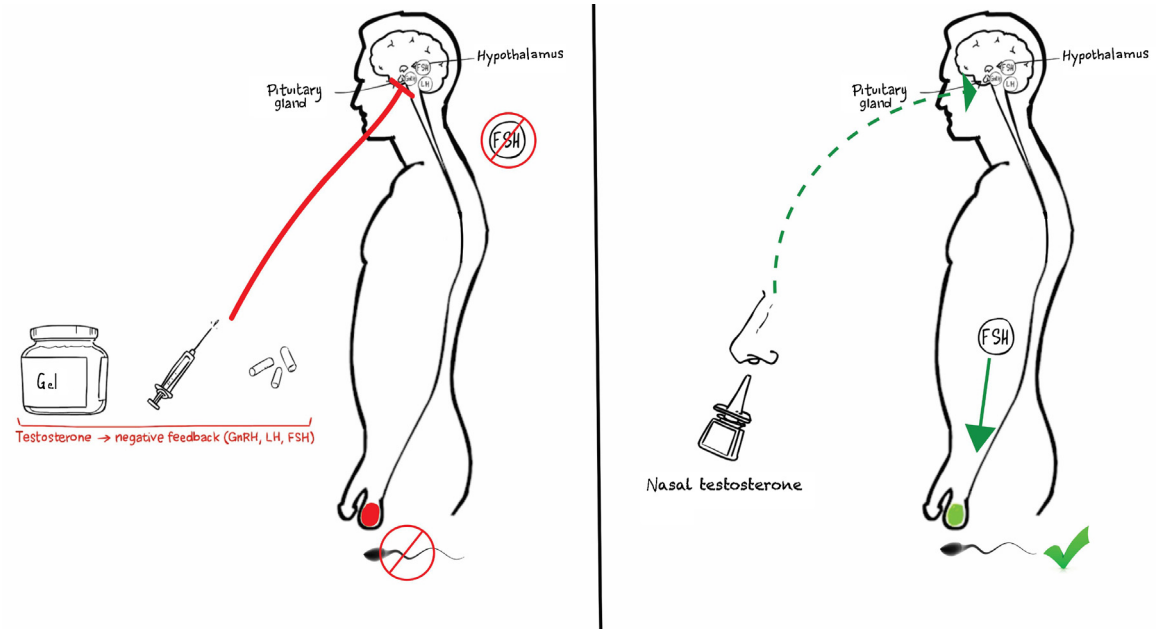

Fig. 1 – Short-acting nasal testosterone appears to preserve follicle-stimulating hormone and luteinizing hormone, thereby maintaining spermatogenesis.
FSH = follicle-stimulating hormone; LH = luteinizing hormone; GnRH = gonadotropin-releasing hormone.

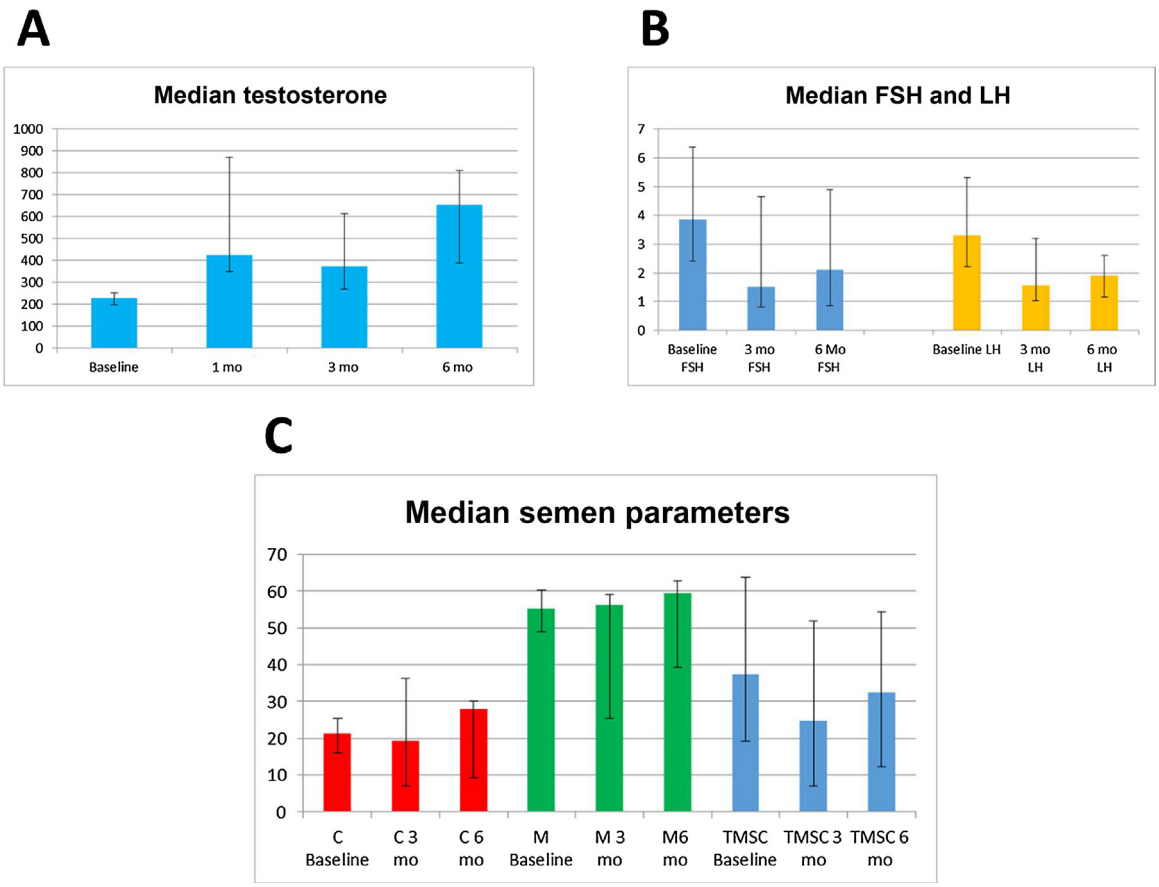

Fig. 2 – (A) Median testosterone levels at baseline and at 1, 3, and 6 mo after therapy with Natesto TID dosing. Note that changes at 1, 3, and 6 mo are significantly increased from baseline. (B) Median follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels at baseline and at 3 and 6 mo after therapy with Natesto TID dosing. Note that the changes in FSH and LH are decreased, but nonsignificant. (C) Median semen analysis concentration, motility, and total motile sperm counts at baseline and at 3 and 6 mo after therapy with Natesto TID dosing. Changes from baseline to 3 and 6 mo are all nonsignificant.
FSH = follicle-stimulating hormone; LH = luteinizing hormone; TMSC = Total motile sperm count.

(196.4–253.1) ng/dl, LH 3.3 (2.2–5.3) IU/ml, and FSH 3.9 (2.4–6.4) IU/ml. Overall, six of the 23 men have dropped out of the study. T levels are available for 15 men at 1 mo. A total of six men have completed 3-mo follow-up, and five men have completed 6-mo follow-up. After 1 mo of therapy, T levels of 14 out of 15 men were above 300 ng/dl, with median of 423.5 (350.0–870.0) ng/dl.

At 3 mo, T levels of four out of six men were above 300 ng/dl, median 374.3 (226.8–614.7) ng/dl (Fig. 2A), LH 1.6 (1.0–3.2) IU/ml, and FSH 1.5 (0.8–4.7) IU/ml (Fig. 2B). Median TMSC changed from 37.5 (17.0–63.9) million at baseline to 24.8 (7.1–52.0) million at 3 mo (Fig. 2C).

At 6 mo, T levels of four out of five men were above 300 ng/dl, median 654.0 (389.5–810.3) ng/dl (Fig. 2A), LH 1.3 (1.1–2.6) IU/ml, and FSH 2.1 (0.9–4.9) IU/ml (Fig. 2B). Median TMSC changed to 32.5 (12.3–54.5) million at 6 mo (Fig. 2C). IIEF-Q15 and SF-36 scores remained statistically unchanged from baseline to 3 mo and 6 mo.

We have accumulated promising initial data demonstrating that Natesto can not only increase serum T but also maintain FSH, LH, and importantly, semen parameters. Natesto has the potential to be “paradigm shifting” in our approach to develop a safe and effective treatment for men with low T who wish to preserve fertility. Understanding factors that influence preservation of spermatogenesis while taking T therapy can enable development of a novel therapeutic strategy for men with low T.

Conflicts of interest: The design and conduct of the study was funded by Aytu Bioscience.

References

[1] Wu FC, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010;363:123–35.

[2] Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract 2006;60:762–9.

[3] Layton JB, Kim Y, Alexander GC, Emery SL. Association between direct-to-consumer advertising and testosterone testing and initiation in the United States, 2009–2013. JAMA 2017;317:1159–66.

[4] Ullah MI, Riche DM, Koch CA. Transdermal testosterone replacement therapy in men. Drug Des Devel Ther 2014;8:101–12.

[5] Amory JK, Chansky HA, Chansky KL, et al. Preoperative supraphysiological testosterone in older men undergoing knee replacement surgery. J Am Geriatr Soc 2002;50:1698–701.

[6] Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med 2004;350:482–92.

[7] Kim ED, McCullough A, Kaminetsky J. Oral enclomiphene citrate raises testosterone and preserves sperm counts in obese hypogonadal men, unlike topical testosterone: restoration instead of replacement. BJU Int 2015;117:677–85.

[8] Alder NJ, et al. Combination therapy with clomiphene citrate and anastrozole is a safe and effective alternative for hypoandrogenic subfertile men. BJU Int 2018.

[9] Dadhich P, Ramasamy R, Scovell J, Wilken N, Lipshultz L. Testosterone versus clomiphene citrate in managing symptoms of hypogonadism in men. Indian J Urol 2017;33:236–40.

[10] de Ronde W, de Jong FH. Aromatase inhibitors in men: effects and therapeutic options. Reprod Biol Endocrinol 2011;9:93.

[11] Rogol AD, Tkachenko N, Bryson N. Natesto a novel testosterone nasal gel, normalizes androgen levels in hypogonadal men. Andrology 2016;4:46–54.

[12] Conners W, Morgentaler A, Guidry M, Westfield G, Bryson N, Goldstein I. MP 89-06 Preservation of normal concentrations of pituitary gonadotropins despite achievement of normal serum testosterone levels in hyopgonadal men treated with a 4.5% nasal testosterone gel. J Urol 2017;197:e1204.