From Two Open-Label Randomized Clinical Trials of Testosterone Pellets, Injections, and Intranasal Gel in Hypogonadal Men

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Introduction & Objective: Exogenous testosterone (T) replacement therapy (TRT) is typically long-acting and can potentially cause infertility in a majority of men due to suppression of HPG axis. Intratesticular testosterone is vital for spermatogenesis and can be reliably evaluated with serum 17-hydroxyprogesterone (17-OHP). Based on this observation, we hypothesized that we used serum 17-OHP as a serum biomarker for evaluating intratesticular T in men receiving TRT. We hypothesized that long-acting TRT will have a significant impact on suppressing HPG axis as compared to short-acting preparations. We evaluated data from two simultaneous open-label, randomized, two-arm clinical trials amongst different treatment preparations (Trial I) subcutaneous T pellets and (Trial II) Intranasal Testosterone (Natesto) or Intramuscular Testosterone cypionate (TC).
Subject & Methods: Hypogonadal men (2 AM serum T < 300 ng/dL assayed by LC-MS/MS) aged 18-65 years were randomized into open-label randomized clinical trials. Eligible subjects received: 800mg subcutaneous Testopel T pellets (n=47); or 11mg TID Intranasal testosterone (Natesto) (n=10) or 200mg x 2 weeks TC (n=10) for 2 months. Serum T and 17-OHP were collected at baseline and after 2 months of therapy. Data are presented as a post-hoc analysis of the two randomized clinical trials and reported as the median and interquartile range [25^{th}-75^{th}], paired sample analysis (baseline versus follow-up) was performed with the Wilcoxon test to determine change during time within the different TRT modalities, with $p<0.05$ considered significant.
Results: Median change for serum T between baseline and 2mo follow-up to subcutaneous T pellets was 542 [454-757] ng/dL, Intranasal Testosterone 706 [517-1010] ng/dL, and TC 525 [280-712]ng/dL.; 96% of subjects in each trial achieved mean T concentrations in the eugonadal range. We demonstrated that serum T levels were within normal range among men receiving the various therapies. As expected, we found a statistically significant decrease amongst the different T preparations in serum 17-OHP. Longer acting T preparations such as T pellets and TC demonstrated the greatest decrease in 17-OHP, from 41 [20.3-65.6] to 14 [10.3-20.8] ng/dL and 80 [48-121] ng/dL to 20 [17-36] ng/dL ($p<0.001$), respectively. Shorter acting T preparations such as Natesto demonstrated a statistically significant decrease in 17-OHP, from 52.5 [26-67] ng/dL to 26.5 [18-39.8]ng/dL ($p=0.007$), but to a lesser extent as compared to the longer-acting preparations.
Conclusions: Natesto, and other short acting forms of TRT may help hyogonadal men maintain Intratesticular T that is critical for maintaining spermatogenesis. The differential effects of TRT on intratesticular T based on their half-lives is novel and should be considered during the decision making for hypogondal men who wish to preserve fertility and / or testis size.

Reproductive Endocrinology

MALE REPRODUCTIVE HEALTH

Impact of Testosterone Therapy on Hematocrit and Polycythemia: Evaluation of Data From Two Ongoing Open-Label Randomized Single-Center Clinical Trials

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Introduction & Objective: Testosterone (T) replacement therapy (TRT) is the mainstay treatment for male hypogonadism. The most commonly reported adverse event among men using TRT is polycythemia. What is unknown is whether the short-acting vs. long-acting testosterone preparations have different effects on hematocrit. We hypothesized that short-acting testosterone therapy will be physiologic and have lesser effect on hematocrit compared to long-acting TRT. We evaluated data from two simultaneous ongoing open-label, randomized, two-arm clinical trials to evaluate the impact of TRT on Hematocrit and compared prevalence rates of polycythemia among subcutaneous T pellets (long-acting) and Intranasal Testosterone (Natesto) or Intramuscular Testosterone cypionate (TC) (short-acting).
Subject and Methods: Hypogonadal men (2 AM serum T < 300 ng/dL assayed by LC-MS/MS) aged 18-65 years were randomized into open-label randomized clinical trials. Eligible subjects received: Trial 1: 800mg subcutaneous Testopel T pellets; Trial 2: 11mg TID Intranasal testosterone (Natesto) or 200mg x 2 weeks TC for 2 months. Serum T, Hematocrit (HCT), and prevalence of polycythemia (as defined as HCT >50%) were collected at baseline and after 2 months of therapy. Data are presented as a post-hoc analysis of the two randomized clinical trials and reported as median and interquartile range [25^{th}-75^{th}], paired sample analysis (baseline versus follow-up) was performed with the Wilcoxon rank test to determine change during time within the different TRT modalities, with $p<0.05$ considered significant.
Results: Median change for serum T between baseline and 2mo follow-up to subcutaneous T pellets was 542 [454-757] ng/dL, Intranasal Testosterone 706 [517-1010] ng/dL, and TC 525 [280-712]ng/dL. T pellets showed a statistically significant increase in HCT from 44.6 [42.0-46.6] to 46.7 [42.6-48.9] ($p<0.001$), with a prevalence of 7/47 (14%) men developing polycythemia. A safety trigger for HCT greater than 54% occurred in 2/47 (4%). The treatment effect was independent of baseline serum testosterone. TRT with Natesto decreased HCT, from 43.4 [41.6-46.1] to 43.4 [40.6-46.5], however not statistically significant ($p=0.262$). TC statistically increased HCT from 41.6 [40.3-43.1] to 43.8 [43.5-47.4] ($p=0.018$), with 0% of men developing polycythemia in both groups.
Conclusions: Long acting TRT appears to increase hematocrit compared to short-acting testosterone therapies. Treatment of hypogonadal men with Intranasal T Natesto and testosterone cypionate successfully achieved target serum T level and maintained HCT levels. Longer-term durability and safety effects of the intervention remain to be further investigated.