Testosterone replacement in androgen insensitivity: is there an advantage?

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Provenance: This is an invited Editorial commissioned by the Section Editor Jianqing Tian (Department of Endocrinology, Xiamen Humanity Hospital, Xiamen, China).


doi: 10.21037/atm.2018.10.73

View this article at: http://dx.doi.org/10.21037/atm.2018.10.73

Androgen insensitivity syndrome (AIS) is the most common etiology of 46,XY disorders of sex development (DSD) (1). In the complete phenotype (CAIS), affected individuals present typically female external genitalia at birth, are assigned as female and present psychosexual development in agreement with sex assignment (2). In CAIS, bilateral gonadectomy is necessary either due to inguinal hernia at childhood or to avoid germ cell tumor development (3). The consequence of bilateral gonadectomy is the need of oestrogen replacement as expected for matched-age women. However, despite an adequate hormonal replacement with estrogens, some CAIS women complained about reduced psychological wellbeing and sexual satisfaction after bilateral gonadectomy (4,5).

Birnbaum et al. designed a clinical trial to answer the question: is testosterone able to improve wellbeing and sexual functioning in patients with CAIS? That question was based on evidence that some sexual behavior brain activation is independent of a functioning androgen receptor and depends on the conversion of testosterone into estrogen by aromatase (6,7).

The health-related quality of life (HRQoL) and mental HRQoL (MHRQoL) were measured with the standardized SF-36 German version, a multipurpose and validated short-form survey which measure eight health domains (physical functioning, vitality, social functioning, role-physical, role-emotional, bodily pain, mental health, general health) and psychometrical physical and mental health summary measures. The Brief Symptom Inventory (BSI), which is an instrument that evaluates psychological distress and psychiatric disorders covering nine symptom dimensions, was used to assess psychological wellbeing. Sexual functioning was measured with a German version of the Female Sexual Function Index (FSFI), a multidimensional
self-report instrument for assessing the key dimensions of sexual function in women. This questionnaire provides scores on six domains of sexual function (desire, arousal, lubrication, orgasm, satisfaction, and pain) as well as a total score.

Testosterone, estradiol, LH, FSH and urinary steroid metabolites were measured at baseline, after the run-in phase and during the treatment, both for treatment monitoring and for compliance estimative.

There was no significant difference in the effect of oestradiol and testosterone on mental health scores or physical summary scores. The MHRQoL and physical HRQoL scores did not differ significantly from baseline either for testosterone or oestradiol replacement. Wellbeing evaluated by BSI scores showed that the patients enrolled had psychological distress at beginning of the trial. Nevertheless, there's no significant difference regarding BSI scores for psychological wellbeing between two groups.

With regard to sexual functioning, the mean value of FSFI score at baseline was 15.78, which is consistent with a low prevalence of satisfactory sexual functioning among those CAIS individuals before treatment. Both hormone-replacement therapies increase the FSFI score from baseline to 19.3 (under oestradiol) and to 21.5 (under testosterone). These increments in FSFI scores were significant from basal FSFI score but it was not significant between each other. The mean FSFI total scores for sexual functioning were higher for testosterone than oestradiol treatment in all sexual domains (except by sexual satisfaction) but statistical significance only occurred in the desire domain (P=0.018).

Regarding safety, three patients dropped out because of adverse events. One patient had fibrous mastopathy receiving oestradiol during run in phase (classified as a serious adverse event). The other two side effects (episodes of depression and hot flush symptoms) occurred in patients receiving testosterone.

In summary, at the end of the study the difference of FSFI total score between both groups was not significant. Although, testosterone was superior to oestradiol in the improvement of sexual desire in the FSFI sub analysis (analysis of each domain) there were no differences on safety between both treatments.

The authors concluded that testosterone was well tolerated and safety as estradiol and it could be an alternative hormone-replacement therapy for patients with CAIS, especially when sexual desire is reduced.

It has been demonstrated that sexual life of 46,XY DSD people is affected for many reasons. However, the results of studies on quality of sexual life are inconsistent, in part either due to the lack of questionnaire on sexual life specific for DSD and for the heterogeneity of the DSD etiologies enrolled in previous studies (5,9,10).

The Birnbaum et al. clinical trial is very interesting because it is the first clinical trial designed for disorders of sexual development individuals. In addition to contributing results of efficacy, this study expands knowledge about the role of androgens in human sexuality. However, it is necessary to pay attention to some points: the sexual improvement by testosterone seems to be related to sexual desire, which was not enough to improve sexual satisfaction. The benefits of steroid replacement in bone integrity and cardiovascular protection are well-established with estrogen replacement but it is unknown regarding testosterone. The shorter period of therapy (6 months) preclude the conclusion of long-term safety.

Although testosterone could be an alternative hormone therapy for patients with CAIS, long term follow-up, assessment of impact on other psychological issues and on bone metabolism and cardiovascular protection are necessary to consider testosterone replacement in CAIS in clinical practice.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Batista RL, Mendonca BB. Testosterone replacement in androgen insensitivity: is there an advantage? Ann Transl Med 2018;6(Suppl 1):S85. doi: 10.21037/atm.2018.10.73