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Mini review

Introduction to Testosterone Preparations for Treatment of Hypogonadism

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Introduction

In males, testosterone (T) controls several important functions including sperm production, sex drive, muscle mass and fat distribution, bone density and red blood cell production, fat and sugar metabolism as well as mood and cognition. During puberty, luteinizing hormone (LH) and follicle stimulating hormone (FSH) start being produced by gonadotropes of the anterior pituitary gland. FSH is critical for spermatogenesis, while T production is regulated in the testes by LH. The action of T is via the androgen receptor located in the cytoplasm and nucleus of target cells. Starting with the fourth or fifth decade of life total T concentrations begin to decline progressively by approximately 1% per year from an average between 270 and 1070 ng/dL, while bioavailable testosterone is approximately 110–575 ng/dL in men aged 18–69. Deficiency or absence of this hormone, which could either be of primary (originating in the testes) or secondary (a problem of the hypothalamus or pituitary gland) origin, seen in combination with characteristic symptoms such as impaired libido with loss of sexual function, regression of secondary sex characteristics, low muscle mass or decreased bone density is defined as hypogonadism.

Apart from age-related reduction in testosterone concentrations, hypogonadism may also result because of autoimmune or genetic disorders, accidents, infection, prolonged exposure, to heavy metals or alcohol, radiation, tumors and chemotherapy [1], and obesity [2]. A wide range of data from several cross-sectional studies indicate that hypogonadism may affect between 17.2% and 38.7% of middle- and older-aged men [3-5]. The primary approach for management of this condition is physiological testosterone replacement therapy (TRT). Testosterone formulations have been available to patients since the 1930s when male hypogonadism was treated with exogenous testosterone in the form of implantable testosterone gel patches, followed in the 1980s, by injectable preparations. Other means of testosterone delivery use the transdermal route (genital or non-genital patches or gel) and offer numerous advantages over other delivery routes including ease of administration and/or cessation of therapy and the achievement of sustained drug plasma levels [1,6].

These systems have the advantage of mimicking the normal circadian rhythm of T, peaking in the morning and declining slowly toward the evening [7-9]. These transdermal delivery systems may, however, cause moderate to severe skin reactions due to the T delivery systems used, regarding T patches, while caution is advised regarding T gels to avoid inadvertent exposure to women

and children [9-12]. Furthermore, T absorption, via the transdermal route, can vary greatly between individuals, and they require daily application, which some patients may not adhere to. Some of the measures taken to overcome these limitations came in the form of chemical modifications of the testosterone molecule, which allowed for oral delivery routes such as testosterone capsules, trans buccal patches or sublingual administration. Some of these formulations proved ineffective due to the first-pass effect of the liver, or, in case of 17 alpha-alkylated derivatives such as methyltestosterone (MeT), caused hepatotoxicity.

Oral T was reported to have stimulatory effects on hepatic microsomal enzyme systems in in vitro studies, and to be associated with the development of peliosis hepatis or hepatocellular carcinoma [13-16]. Testosterone injections delivered via the intramuscular route are absorbed directly into the blood stream and bypass the first-pass effect of the liver, thus avoiding hepatotoxicity. To date, these formulations remain the most cost-effective and widely used T therapy. The first preparations available were the short-acting formulations of T esterified with fatty acids dissolved in an oil-based vehicle, such as testosterone cypionate and testosterone enanthate (TE), testosterone propionate, and testosterone cyclohexane carboxylate. However, they have an effective duration of action of 1–2 weeks which brings fluctuations in injection delivery and gives greater variability and subjectivity of symptoms in patients [17,18]. Despite the pharmaceutical availability, of approximately 85 years, the therapeutic use of T has been hampered due to the low bioavailability following both oral and parenteral administration, associated with a short circulating half-life [19].

In search of a medium-term solution, with improved efficacy, balanced symptoms and reduced side-effects, long-acting testosterone undecanoate (LA-TU) with intramuscular administration was developed, initially in the 70s in China [20,21], and subsequently, due to some problems at the injection site, redeveloped by Jenapharm GmbH & Co. KG, a subsidiary of Schering AG in Berlin, Germany [22]. Intramuscular TU is currently prescribed in the USA under the trade name Aveed® (Endo International plc, Dublin, Ireland), in Europe, Latin America, and Asia under the trade name Nebido® (Bayer HealthCare Pharmaceuticals, Berlin, Germany) and in Australia under the trade name Reandron 1000® (Bayer HealthCare Pharmaceuticals, Berlin, Germany).

Impact of TU Therapy on Patient-Focused Perspectives

As androgen replacement therapy is normally associated with long-term medical conditions, therapy often extends over many decades, making patient compliance of utmost importance. Prior to TU administration, patients diagnosed with hypogonadism report a significantly reduced QoL, affected by symptoms including low libido, erectile dysfunction, infertility, gynecomastia, hot flashes, or as more non-specific symptoms such as low energy, sleep disturbance, depression or labile mood, impaired cognition, osteoporosis, and loss of muscle mass or increased BMI [25-27]. Regarding patient compliance and uptake, a major advantage of TU injections is the reduced frequency of visits allowing for reflection on efficacy and safety of TU therapy, when adjustment of the injection interval is required (most often by prolonging to every 13–14 weeks), as compared to almost bi-monthly visits for TE therapy. Furthermore, as TU only requires four injections per year compared to 26 injections per year with TE, there is a greater compliance rate in TU treated patients.

Conclusion

Reviews of the literature looking at the efficacy and safety of injectable TU treatment have concluded that this type of treatment has a significant positive impact on the quality of life (QoL), symptoms of hypogonadism and associated comorbidities in men. Injectable TU offers the possibility of a therapeutic intervention just four to five times per year freeing the patient, at least partially, from having a chronic condition, thus maintaining a positive, active role in self-caring [23,24].

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