Retrospective Investigation of Testosterone Undecanoate Depot for the Long-term Treatment of Male Hypogonadism in Clinical Practice

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ABSTRACT

Introduction. Testosterone undecanoate depot (TUD) administered intramuscularly is an effective form of testosterone replacement therapy (TRT) for male hypogonadism. Because of the ease of administration, TUD therapy may be preferable to subcutaneously implanted extended release T pellet implants (TI).

Aim. The primary objective was to retrospectively assess the efficacy and safety of long-term (≥2 years therapy) TUD therapy in the clinical setting. The secondary objective was to retrospectively compare TUD with TI therapy.

Methods. Retrospective data were collected from the Waikato Hospital Endocrine Database for 179 hypogonadal men treated with TUD for ≥2 years from 1998–2011, with 124 of these men receiving previous TI therapy.

Main Outcome Measures. The main outcome measure for efficacy was serum trough total testosterone (TT), and for safety an increase in hemoglobin (Hb) and/or hematocrit (Hct), rise in prostate-specific antigen (PSA) and/or prostatic biopsy and alteration in body mass index and lipid profile. Additional outcome measures were changes in the dosing and/or interval regimens for TUD therapy.

Results. Overall, 72% of trough TT levels were in the normal range for TUD therapy compared with 53% of trough TT levels during TI therapy. TUD therapy was well tolerated with 162 men (90.5%) completing 2 years of treatment, and only seven men (3.9%) stopping TUD because of adverse effects. A rise in Hb and/or Hct occurred in 25 men (14%), and a significant rise in PSA in 20 men (13%) at some stage during TUD therapy. At 2 years, 91% of men received the standard 1,000 mg TUD dose with 66% at the standard dosing interval of 10–14 weekly.

Conclusions. TUD is an efficacious, safe, and well tolerated form of TRT, and individual optimisation of the dose and/or interval is only required in the minority of men. Particularly given the ease of administration, TUD was the preferred TRT for both patients and clinicians. **Conaglen HM, Paul RG, Yarndley T, Kamp J, Elston MS, and Conaglen JV. Retrospective investigation of testosterone undecanoate depot for the long-term treatment of male hypogonadism in clinical practice. J Sex Med 2014;11:574–582.**

Key Words. Hypogonadism; Testosterone Replacement; Testosterone Undecanoate Depot; Testosterone Deficiency Syndrome

Introduction

Male hypogonadism is a clinical syndrome defined as failure of the testes to produce physiological levels of testosterone (T) and normal numbers of spermatozoa due to disruption of the hypothalamic-pituitary-gonadal axis [1]. Primary hypogonadism results from testicular disease or injury, whereas secondary hypogonadism is due to hypothalamic-pituitary dysfunction such as that resulting from chronic disease or pituitary tumors and/or their treatment. Male hypogonadism is a common endocrine disorder affecting 5.6% of men aged between 30–79 years with prevalence increasing with age [2]. The diagnosis requires the presence of clinical features of hypogonadism associated with two early morning serum total testosterone (TT) levels below the reference range (RR). Serum TT levels must be performed close to 0800 hours because of the marked diurnal variation of testosterone particularly in younger men [3]. Two low serum TT measurements are

required to confirm the diagnosis because of the high intraindividual day-to-day variation of serum testosterone [4,5].

A recent meta-analysis of testosterone replacement therapy (TRT) reported significant increases in hemoglobin (Hb) and hematocrit (Hct), and decreases in high-density lipoprotein (HDL) levels in men [6]. There were no significant changes in total cholesterol (TC), low-density lipoprotein (LDL), or triglyceride (TG) levels [6]. In concordance with previous reviews, TRT was not associated with a significant increased risk of prostate cancer, prostate biopsy, benign prostatic hypertrophy (BPH), or a significant rise in serum prostate-specific antigen (PSA) levels [6,7]. However, limitations of this meta-analysis were that the majority of the studies were small (only 5 studies included more than 100 men) and follow-up periods were comparatively short (only five studies had more than 1 year of follow up). Positive effects of TRT have been documented with respect to depression and sexual function in hypogonadal men with metabolic syndrome [8] and men with type 2 diabetes [9], those with late onset hypogonadism [10], and a series of cases with venous leakage [11].

The aims of TRT in hypogonadism are to ameliorate the clinical features and restore serum TT to physiological levels [12]. As treatment with TRT for hypogonadism is typically lifelong and needs to be safe, effective, and convenient with minimal impact on lifestyle, the frequency of administration, mode of delivery, efficacy, and side-effect profile are important. Although TRT has been available for over 70 years, in recent years, newer treatment modalities have become available and offer significant benefits in terms of efficacy and patient satisfaction. Current TRT modalities include oral testosterone capsules, transdermal testosterone patches or gel, subcutaneously implanted extended release pellets, intramuscular injections with mixed testosterone esters every two to four weeks, or testosterone undecanoate depot (TUD) every three months.

All of these TRT options are available in New Zealand, although the only publicly funded options are capsules, patches, and mixed esters. Because of side effects from patches, poor oral bioavailability of capsules, and the peaks and troughs from mixed esters, we have administered subcutaneously implanted extended release T pellet implants (TI) for hypogonadal men since 1998 as a safe and effective form of TRT [13]. Insertion of TI requires significant input of specialized staff time and equipment. Adverse effects of TI in addition to those of TRT include a 5–10% risk of extrusion with a lesser risk of infection and bleeding [14,15]. Significant scarring and fibrosis from pellet insertion are rare but mild palpable subdermal fibrosis is common and may be disconcerting to patients [16]. TUD injections have been available in Europe, Asia, and Australasia since 2004 and have been shown to be an effective and well-tolerated form of TRT [17,18]. TUD has the benefit of easier intramuscular administration with a flexible regimen of typically 1,000 mg at 12 weekly intervals [17]. Previous reports in the literature have shown TUD to be equally efficacious with a similar adverse effect profile to the earlier injectable T esters (e.g., T enanthate); however, TUD is typically preferred by patients and clinicians alike, as its long-acting depot formulation requires administration only four times per year and it removes the peaks and troughs associated with injectable T ester therapy [19–22]. We elected to trial TUD therapy as an alternative to extended release TI because of the evidence supporting the use of TUD and its ease of administration vs. TI therapy.

Aims

The primary objective of this retrospective study was to assess the efficacy and safety of long-term (>2 years therapy) TUD therapy in the clinical setting for a relatively large cohort of hypogonadal adult males. The outcome measurements were based on efficacy (trough serum TT) and safety—increase in Hb and/or Hct, rise in PSA and/or prostatic biopsy, alteration in lipid profile in addition to dosing regimens of TUD. A secondary objective was to retrospectively compare TUD with TI therapy.

Methods

Data Collection

Data was obtained from the Waikato Hospital Endocrine Unit database, which contains the demographic and clinical information of all treated hypogonadal men from 1998–2011. Treatment details, body mass index (BMI), laboratory results, and complications were recorded. Waist and hip circumference data were not available.

Patient Selection

We identified a total of 254 men with hypogonadism (based on two 0800 hours serum TT levels