Dr. Joseph Varon - Research Inquiry #18

Safety of Testosterone in B-cell Type Chronic Lymphocytic Leukemia | 17.04.2024

Research Inquiry

Is testosterone supplementation safe in a patient with a history of chronic lymphocytic leukemia (B-cell type)?

Conclusion

- **Chronic lymphocytic leukemia (CLL) is not classified as hormone-dependent cancer, and there appears to be no clear link between testosterone replacement therapy and the progression or relapse of CLL.**
- **Recent data shows that testosterone is relatively safe regarding ischemic cardiovascular events. However, testosterone supplementation has been associated with an increased incidence of arrhythmias and atrial fibrillation.**
- **Testosterone was not found to cause diabetes-related adverse events. Furthermore, testosterone supplementation has been associated with improved outcomes for older patients with hypogonadism.**

- **Patient-Specific Drug interactions - testosterone is not expected to interact with first-line and second-line treatments for CLL B-cell type. Possible additive steroidal side effects may occur when combined with systemic adreno-corticotropic hormones and steroid treatment.**
- **Testosterone replacement therapy's main side effects are local irritation and skin reactions, mood fluctuations, and increases in serum PSA and hematocrit levels.**

Meta Medical Findings

Testosterone and CLL

Chronic lymphocytic leukemia (CLL) is traditionally not categorized as a hormone-dependent cancer[1]. Research published in Annals of Hematology (Q1, Impact factor 3.5) in 2018[1] investigated the effects of sex hormones on hematological malignancies in a single center. Its findings indicated that higher levels of luteinizing hormone (LH) were associated with shorter treatment-free survival (TFS) in male patients. It is known that LH secretion from the pituitary is influenced by testosterone, which typically decreases with age, leading to increased LH levels in older men. However, the study did not confirm a direct link between testosterone levels and the progression of CLL.

No other studies have been found regarding the connection between testosterone replacement therapy and the progression or relapse of CLL.

Safety of testosterone

This part of the report will focus on assessing the safety of testosterone, taking into account the patient's pre-existing health conditions.

- **Cardiovascular-related adverse effects**
  - **The TRAVERSE trial: Cardiovascular safety of testosterone replacement therapy**[2] - A study published by the New England Journal of Medicine (Q1, Impact factor 158.5) in 2023, aimed to investigate the occurrence of any adverse event from a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

    Study design and population: The study was a randomized, double-blind, placebo-controlled trial. It involved 5,246 men aged 45 to 80 who either had preexisting cardiovascular disease or were at high risk of developing it. The primary safety endpoint was the first occurrence of any component of major adverse cardiac events, a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis

    Intervention: study participants were randomly assigned to receive either a daily transdermal 1.62% testosterone gel or a placebo for a mean of 22 months.

    Results: Patients were treated for an average of 21.7 months, and followed for 33 months on average. In the testosterone-treatment group there were 191 major cardiovascular events, including non-fatal myocardial infarctions, non-fatal strokes, and cardiovascular-related deaths, compared to 203 such events in the placebo group (7.0% vs. 7.3%; hazard ratio, 0.96; 95% CI; P<0.001). No significant differences were found in the occurrence of major cardiac events. However, the treatment group had increased adverse effects - see table.

Adverse effect	Treatment group	Placebo group
Non Fatal arrhythmias requiring intervention	134 patients (5.2%)	87 patients (3.3%)
Atrial fibrillation	91 patients (3.5%)	63 patients (2.4%)
Acute kidney injury	60 patients (2.3%)	40 patients (1.5%)

- **Adverse cardiovascular events and mortality in men during testosterone treatment, a meta-analysis**[3] - A meta-analysis, published in The Lancet Health Longevity journal in 2022 (CRD42018111005, Q1, impact factor 13.1), investigated cardiovascular adverse events associated with testosterone treatment among men. The literature search identified 109 placebo control trials that met inclusion criteria up to 08/2018. The analysis included a total of 5601 patients.

  The authors concluded that there is no evidence that testosterone increased short-term to medium-term cardiovascular risks in men with hypogonadism (OR 1.07 [95% CI 0.81–1.42]; p=0.62). As for specific cardiovascular adverse events during testosterone treatment *vs* placebo treatment - see table.

Adverse effect	Treatment Group Occurrence	Placebo Group Occurrence
Arrhythmias	52 patients (31.3%)	47 patients (26.7%)
Coronary artery disease	33 patients (19.8%)	33 patients (18.7%)
Heart failure	22 patients (13.2%)	28 patients (15.9%)
Myocardial infarction	10 patients (6%)	16 patients (9.1%)

It is important to note that interaction tests showed that patient age, baseline testosterone, smoking status, or diabetes status were not associated with higher cardiovascular risk.

Since this publication, one RCT has shown similar findings - the TRAVERSE trial, elaborated above.

- **Type 2 Diabetes mellitus-related adverse effects**

  In the reviewed studies[4] [5] [6], no information was found on adverse events related to diabetes, such as hyperglycemia events, hypoglycemia events, or aggravation of target organ damage. Furthermore, while not in the scope of this research, there are indications that testosterone supplementation may improve some of the diabetes outcomes of patients with low testosterone levels[7].

- **General adverse effects**

  Testosterone replacement therapy is available in various formulations, each with potential specific side effects[8]. Buccal tablets may irritate the gums and oral mucosa, while testosterone patches can lead to skin reactions. Injectable testosterone might cause fluctuations in mood, energy, and libido. Additionally, literature indicates that serum prostate-specific antigen (PSA) levels can increase following testosterone treatment, making it crucial to exclude prostate cancer before initiating therapy.
  Furthermore, testosterone has been linked to erythrocytosis, related to increased hematocrit levels.

Drug interactions of Testosterone

This part of the report will focus on detailing any drug interactions between testosterone and the patient's existing medication regimens.

Drug	Possible interaction
Insulin[9]	A single report (1995) suggested testosterone may enhance the blood glucose-lowering effects of insulin. No further supporting data for this effect was found.
Budesonide[10]	Concomitant use of androgens with adrenocorticotropic hormone or corticosteroids may result in increased fluid retention and edema due to additive steroidal effects. However, no data was found regarding inhalations of budesonide.

Upon a review of the recent literature, no drug interactions were found between testosterone supplements and the following medications: SynjardyXR, Losaratan, Omega-3, Vyvanse, Bupropion, Esomeprazole, Simvastatin, Montelukast, Ropinirole, Toujeo solostar, Ozempic pen, Lyumjev, Ipratropium Bromide, Budesonide, Azelastine nasal spray, and Breztri inhaler.

Additionally, a search was conducted to find potential interactions with both first-line and second-line treatment regimens for BCLL[11]. No interactions were found.

References

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