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Original article

Adverse events during testosterone replacement therapy in 95 young hypogonadal thalassemic men

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Summary. *Background:* Hormonal treatment of hypogonadism in thalassaemia major (TM) is a complex issue due to the co-existence of other contributing factors such as severity of iron overload, associated chronic liver disease and other endocrine complications. *Objectives:* Data about adverse events (AEs) of testosterone replacement therapy (TRT) in hypogonadal males with TM is scarce.We report the adverse events registered during TRT in 95 young patients with TM. *Results:* These AEs included gynecomastia, documented in 41/95 (43.1%) TM patients of mild to moderate severity (90%). Persistent pain in the injection site and local reactions to testosterone (T) skin patch occurred in a third of patients. Priapism was reported in 2 patients on treatment with intramuscular T enanthate. In both patients, substitution with T gel was successful, and no recurrence during the following 24 months was observed. *Conclusions:* Clinicians should exercise caution when considering TRT for hypogonadal men with TM. (www.actabiomedica.it)

Key words: thalassemia major, testosterone therapy, adverse events, gynecomastia, priapism

Introduction

About 40% to 80% of male patients with thalassemia major (TM) experienced pubertal failure, sexual dysfunction and infertility due to hypogonadotropic hypogonadism (HH) (1, 2). Hormonal management of HH in thalassaemia is a complex issue due to the co-existence of other interfering factors such as severity of iron overload, associated chronic liver disease and other endocrine complications (3).

Over the past two decades, significant advances have been made for improving the understanding of the pathophysiology of endocrine complications in patients with TM. Cross-sectional and review papers reported that from 40% to 80% of male TM patients experienced pubertal failure, sexual dysfunction and infertility due to HH (1). However, testosterone replacement therapy (TRT) has numerous benefits that can greatly enhance a patient's quality of life.

Much of the controversy surrounding testosterone therapy stems from intense attention on recent reports suggesting increased risk of venous thromboembolism or cardiovascular events in young and aging men (4-6).

The aim of the present retrospective study was to analyze the adverse events registered during TRT in a group of hypogonadal TM patients, followed in the last 43 years by a single Centre.

An adverse event was defined as an unfavourable medical event that may present during treatment with a pharmaceutical product, which does not necessarily have a causal relationship with the product.

Patients and methods

This retrospective study analysed adverse events registered during TRT in 95 hypogonadal male TM patients with arrested puberty (AP:4.2%), HH

(84.3%) or acquired hypogonadotropic hypogonadism (AHH:11.5%), followed regularly or occasionally at the Pediatric and Adolescent Outpatients Clinic of Ferrara. All patients (age 17-42 years; mean 27.6) were of Italian ethnic origin.

An adverse event was defined as an unfavourable medical event that may present during treatment with a pharmaceutical product, which does not necessarily have a causal relationship with the product.

All patients were evaluated for pituitary-gonadal axis integrity. The diagnosis of HH was based on symptoms and signs of hypogonadism plus the presence of low serum testosterone level measured on at least two occasions, normal prolactin, and low basal pituitary gonadotropin levels (LH and FSH).

Virilization was the primary objective for these TM patients in order to ameliorate their psychological problems related to hypogonadism. Several testosterone (T) formulations were prescribed for their treatment: T intramuscular injections (51.7%), T gel preparations (25.2%), T transdermal patches (12.6%), and T undecanoate given orally (10.5%). The duration of TRT varied from 1-25 years (mean 8.5 years).

Results

Normalization of T levels improved most of the effects due to hypogonadism (sexual infantilism, decreased sense of well-being, loss of libido, erectile or ejaculatory dysfunctions.

The adverse events registered during long-term TRT in 95 patients with TM are reported in table 1. The commonest event was gynecomastia, documented in 41/95 TM patients (43.1%) of mild to moderate severity (90%). Forty six percent of them were HCV-RNA positive. No patient was treated with aromatase inhibitors.

Persistent pain in the injection site and local reactions to T skin patch occurred in some patients.

Priapism was reported in 2 patients on treatment with intramuscular T (100 mg testosterone enanthate, monthly and twice a month). Priapism was not due to supra-physiological levels of testosterone in the serum. One patient (32 years), responded to aspiration of blood from the corpora cavernosa and administration of a sympathomimetic. Acute lower-limb exercise (stair climbing) was effective in the second patient (26

Table 1. Adverse events registered during testosterone replacement therapy in 95 thalassemia major patients (TM) with hypogonadism

Adverse events	TM patients (Numbers and %)
Gynecomastia	41/95 (43.1%)
Persistent pain in the injection site	25/95 (26.3%)
Application site reactions where the skin patch was worn (redness, itching, burning, or hardened skin)	13/22 (13.6 %)
Acne and/or oily skin	8/95 (8.4%)
Mild elevation of liver enzymes	4/95 (4.2%)
Insomnia	3/95 (3.1%)
Frequent urination	3/95 (3.1%)
Excessive libido	2/95 (2.1%)
Priapism	2/95 (2.1%)
Mild elevation of lipids	2/95 (2.1%)
Associated recurrent mild fever	1/95 (1%)
Headache	1/95 (1%)
Deterioration of glucose tolerance (from normal to impaired glucose tolerance)	1/95 (1%)
Elevation of prostate-specific antigen (PSA)	none
Depression	none
Sleep apnea	none
Increased blood pressure	none
Increased appetite	none
Changes in taste or smell	none

years). In both, substitution with T gel was successful, and no recurrence during the following 24 months was observed.

None of the patients had symptoms or signs suggesting venous thromboembolism, associated with use of TRT.

Discussion

Despite recent advances in iron chelation therapy, excess iron deposition in pituitary gonadotropic cells remains one of the major problems in thalassemic patients (1, 7, 8).

Hypogonadism, mostly HH , is usually detected during puberty. In addition, the direct effect of iron, in particular that of Non-Transferrin-Bound Iron (NTBI), on the testes appears to be harmful (9).

Histological examination of testicular tissues from autopsies demonstrated testicular interstitial fibrosis with small, heavily pigmented, undifferentiated seminiferous tubules and an absence of Leydig cells (10).

Early diagnosis and treatment are crucial for normal pubertal development and to reduce the complications of hypogonadism (1, 2). The American Society of Andrology, concluded that men with serum testosterone concentrations below 264 ng/dL (9.2 nmol/L) will usually benefit from testosterone replacement therapy (TRT) (11).

The different goals of T therapy should be summarized by the following: 1. to induce sex-specific secondary sexual characteristics, and then maintain them in adulthood; 2. to optimize pubertal growth spurt and have physiologic body proportions (not to be eunuchoid); 3. to obtain adequate lean muscle mass, fat mass and optimal bone mineral mass accretion; 4. to develop adequate external genital appearance (penile size and scrotum) and internal genitalia growth; 5. to reduce cardio-vascular and metabolic syndrome risk by optimization of lipid profile, and 6. to induce sex-specific psychosocial and psychosexual maturation, and assure normal social/sexual life and well-being (12). However, the risks and benefits of TRT, remain a challenge for providers caring for thalassemic patients.

In this long-term retrospective study, the commonest side effect was gynecomastia, documented in 43.1% of patients. However, the degree of gynecomastia ranged between mild to moderate in severity (90%) and did not necessitate further management. None of the patients received aromatase inhibitor therapy. Aromatase is the enzyme responsible for converting androgens to estrogens and is widely distributed in several tissues such as brain, liver and reproductive tissue. In men, estrogen production occurs mainly by extra testicular aromatization of androstenedione to estrone and of testosterone to estradiol. Therefore, exogenous testosterone through aromatization may increase estradiol production leading to gynecomastia (13).

In addition, the associated presence of chronic liver disease, because of hepatic iron overload and previous viral liver infection (46.4% of TM patients were HCV-RNA positive), may exaggerate and contribute to the relatively high incidence of the gynecomastia in thalassemic patients on TRT. In chronic liver disease there is an increased production of androstenedione by the adrenal glands, increased aromatisation of androstenedione to estrogen, loss of clearance of adrenal androgens by the liver and a rise in SHBG, resulting in gynecomastia (14, 15) (figure 1).

Persistent pain at the injection site and local reactions to T skin patch occurred in about one third of patients. Successful management of cutaneous reactions has been shown to be successful through rotation of application sites, patch placement on the buttocks, trials of alternate brands, a shorter duration of occlusion, and pretreatment of the skin with topical corticosteroids (16).

Although priapism because of TRT is a rare complication, it was reported in 2 of our TM patients on treatment with intramuscular enanthate T. Intramuscular depot injection of testosterone is less expensive and can be administered every 2-4 weeks. A major disadvantage is the strongly fluctuating concentrations of plasma testosterone which are at least 50% of the time not in the physiological range. This also causes supraphysiologic serum testosterone concentrations within 2 to 3 days of injection and a slow decline to subnormal levels within 1 to 2 weeks (12, 17). However, in the two patients, priapism did not appear to be due to supra-physiological levels of testosterone in the serum because of the lower dose used. Treatment of priapism in one patient (32 years old) required aspiration

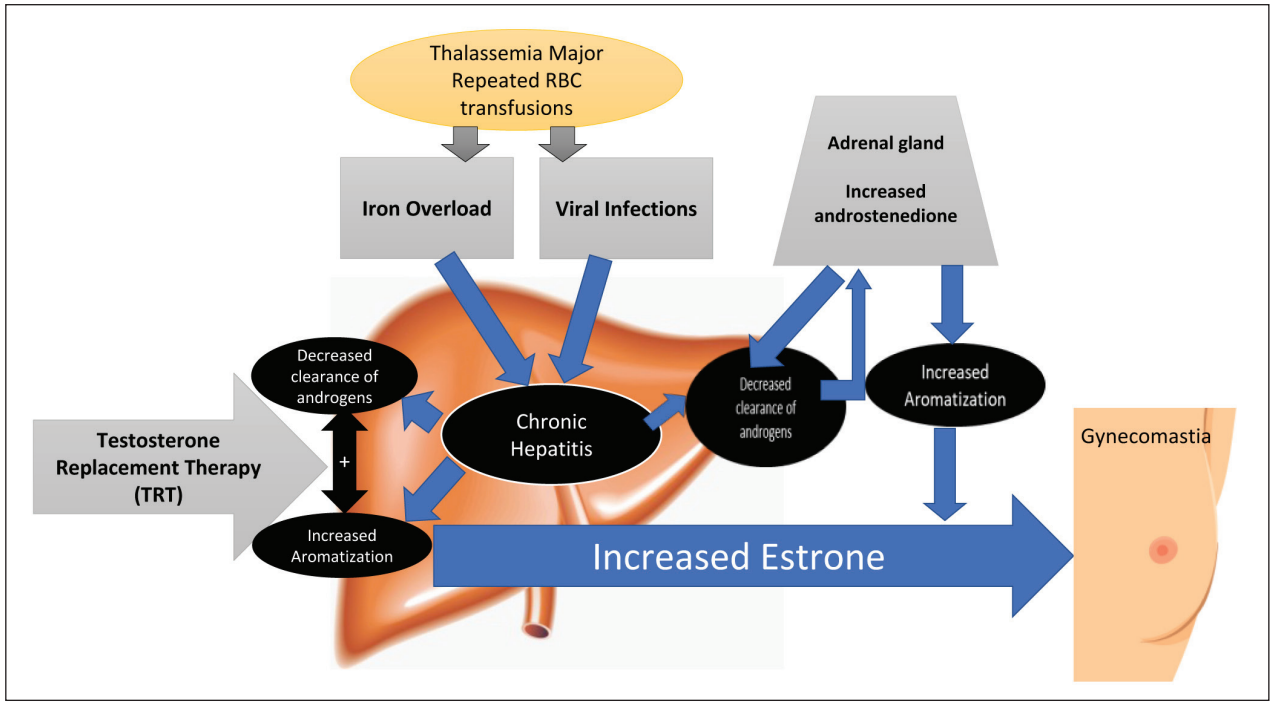

Figure 1. Pathophysiology of gynecomastia in thalassemic patients on testosterone replacement therapy (TRT)

of blood from the corpora cavernosa, to decompress the penis, and administration of a sympathomimetic. Conservative management using acute lower-limb exercise (stair climbing) was effective in the second patient (26 years old) on treatment with 100 mg testosterone enanthate, bimonthly. In both patients, replacement therapy with a different drug formulation (T gel) was successful, and no recurrence developed during the following 24 months.

None of our patients had symptoms or signs suggesting a hypercoagulable state or venous thrombosis. However, various studies reported incidence of thromboembolic event in thalassemia, ranging between 1–29% (18-20). Our group previously reported the incidence of left atrial thrombosis in a 19-year-old adolescent male with TM and diabetes mellitus (6).

In females, randomized controlled trials (RCT) demonstrated that oral estrogen increases venous thromboembolism (VTE) risk in women aged 50 to 59. However, observational studies and meta-analyses suggest that transdermal estrogen therapy does not increase VTE risk, even in women with thrombophilia (21). No RCTs were conducted in thalassemic patients on estrogen or testosterone transdermal therapy. Therefore, VTE is still potential serious side effect that should be kept in mind during TRT.

It appears that TRT improves many negative effects of hypogonadism in our thalassaemic hypogonadal males and in other studies but should be utilized with full awareness of its potential risks.

Measuring serum testosterone to avoid supraphysiological levels of T and monitoring for adverse effects from TRT should also be done. A prostatic specific antigen (PSA) concentration and digital rectal examination should be performed at baseline and at 3 months, 6 months, then yearly after TRT is initiated (11).

Proper and intensive iron chelation is important for decreasing the iron load in the liver and endocrine system. In 14 hypogonadal males on testosterone therapy, seven stopped treatment after intensive chelation of their body iron (22).

Conclusion

Clinicians should exercise caution when considering TRT for hypogonadal men with TM and discuss the benefits and potential risks prior to initiating treatment and monitor any side effects during their use.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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