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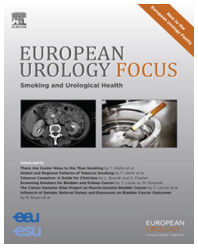

Review – Prostate Cancer

Risk of Testosterone Flare in the Era of the Saturation Model: One More Historical Myth

Yonah Krakowsky, Abraham Morgentaler *

Men's Health Boston, Beth Israel Deaconess Medical Center, Harvard Medical School, Chestnut Hill, MA, USA

Article info

Article history:
Accepted June 8, 2017

Associate Editor:
James Catto

Keywords:
Testosterone
Androgens
Flare
Prostate-specific antigen
Risks
Prostate cancer

Abstract

Context: When luteinizing hormone–releasing hormone (LHRH) agonists were introduced in the 1980s, it was universally believed that the initial transient rise in serum testosterone (T), termed T flare, caused rapid prostate cancer (PCa) growth and led to disease progression, complications, and death. It became routine to offer antiandrogens (AAs) to prevent these risks. However, over the last decade, it has become recognized that androgens have a finite ability to stimulate PCa growth (the saturation model), providing a theoretical challenge to the risks of T flare.
Objective: To review evidence for the risks associated with T flare from a modern perspective, specifically prostate-specific antigen (PSA) flare, disease progression, and spinal cord compression.
Evidence acquisition: An Ovid Medline database search was conducted to identify articles related to "testosterone flare", "disease flare", and "PSA flare" associated with LHRH agonists. The literature review included papers published from May 1, 1980 through May 1, 2016. Key search terms included, luteinizing hormone–releasing hormone, gonadotropin-releasing hormone, and antiandrogens.
Evidence synthesis: Initial administration of LHRH agonists uniformly results in peak increases in serum T by 40–100% on days 2–3, returning to baseline by days 7–8, after which T declines to castrate levels by approximately 2–3 wk. Of six LHRH agonist studies reporting PSA during the period of T flare, five showed no significant rise in PSA despite the presence of advanced disease with mean baseline PSA as high as $\geq$500 ng/ml. Evidence for disease flare was limited to one report of greater bone pain with LHRH agonists alone versus LHRH agonists with AAs. Three other RCTs reported no disease flare. Rates of spinal cord compression were no greater for LHRH agonists alone compared with castration or estrogen treatment. We identified no studies of men treated with LHRH agonists versus placebo/no treatment to assess the effects of LHRH agonists compared with the natural history of advanced PCa.
Conclusions: Although T flare has been considered risky for 30 yr, a modern review of the evidence collected primarily in the 1980s and 1990s fails to support this view. Specifically, T flare does not appear to be associated with significantly increased PSA, disease progression, or adverse events, even in men with widely metastatic disease. These results are consistent with the saturation model, first introduced in 2006. There seems little value in adding AA to LHRH agonists, except possibly for men with extensive vertebral metastases and serum T concentrations well below the saturation point of approximately 250 ng/dl (8.7 nmol/l).
Patient summary: A review of the literature reveals no evidence for increased risks associated with testosterone flare from the initiation of luteinizing hormone–releasing hormone (LHRH) agonists. This appears to be an unsupported belief from an earlier era when our understanding of testosterone's relationship to prostate cancer was less sophisticated. Except in rare instances, there appears to be no need to use an androgen blocker when beginning treatment with LHRH agonists.

* Corresponding author. Men's Health Boston, 200 Boylston St., Suite A309, Chestnut Hill, MA 02467, USA. Tel. +1-617-277-5000; Fax: +1-617-277-5444.
E-mail address: dr.morgentaler@menshealthboston.com (A. Morgentaler).

http://dx.doi.org/10.1016/j.euf.2017.06.008
2405-4569/

1. Introduction

For approximately 30 yr it has been believed that the transient rise in serum testosterone (T) that occurs with the administration of luteinizing hormone–releasing hormone (LHRH) agonists, called T flare, causes rapid prostate cancer (PCa) growth, leading to disease progression, urinary retention, increased bone pain, fractures, vertebral collapse with spinal cord compression, and death. To prevent these risks, it has been longstanding routine practice to combat the effects of T flare by adding antiandrogens (AAs) upon initiation of LHRH agonists. Yet, it has been a decade since it was first noted [1] that prostate-specific antigen (PSA) values failed to increase during T flare in two highly cited studies [2,3]. In light of major advances in our understanding of the relationship of androgens and PCa, we believe that it is time to re-examine the validity of flare as a risk of LHRH agonist treatment.

The belief that T flare was dangerous arose in the 1980s at a time when the androgen hypothesis was universally accepted [4]. The androgen hypothesis assumed that PCa growth was directly and linearly related to serum T concentration, summarized as follows: "More testosterone leads to more rapid PCa growth." Features of the androgen hypothesis included the beliefs that high T caused PCa, low T was protective against development of PCa, and T administration in the presence of known PCa was like "pouring gasoline on a fire." Modern data show that each of these concepts is incorrect [5,6].

The key to our modern understanding of the relationship of androgens and PCa is the saturation model, first introduced in 2006 and refined in 2009 [7]. Briefly, the saturation model is based on substantial evidence that PCa growth is exquisitely sensitive to changes in serum androgens at very low concentrations but then reaches a maximum, called the saturation point, above which further increases in serum T cause little or no additional androgenic PCa stimulation (see Fig. 1). This maximal stimulation threshold is reached at a relatively low value, with human data suggesting a prostate saturation point of approximately 250 ng/dl (8.7 nmol/l). In a 6-mo placebo-controlled T gel study, men whose baseline T was below 250 ng/dl demonstrated a significant rise in PSA, whereas those with baseline T concentrations above this value demonstrated no PSA increase [8]. A registry study reported similar results, supporting 250 ng/dl as the saturation point [9]. The saturation model thus explains the dramatic changes in PSA when serum T concentrations are manipulated into or out of the castrate range, and also why administration of supraphysiological doses of T to healthy volunteers for periods up to 9 mo resulted in no increase in PSA or prostate volume [8].

Initial administration of LHRH agonists reliably causes a transient rise in serum T, with peak T values observed at 2–4 d followed by a reduction to baseline values by 7–8 d, and achievement of castrate levels by 2–4 wk [10]. Most studies demonstrate an increase in peak serum T concentrations by 40–100% above baseline during T flare. In the 1980s and 1990s, when the androgen hypothesis was universally accepted, any adverse clinical effects seen within 1–2 mo of LHRH agonist administration was typically attributed to T flare. Within this conceptual framework, it was logical to administer AAs for the 1 st month to prevent the dangers of T flare. Today, however, given our knowledge that there appears to be a finite ability of androgens to stimulate PCa growth, it is important to ask, how strong is the evidence that T flare is associated with PCa progression or major adverse events?

The goal of this study was to review the evidence regarding the effects and adverse events associated with T flare, much of it performed in the 1980s and 1990s, and to provide a critical reappraisal from a modern perspective that incorporates advances in understanding of the biological relationship of PCa and androgens.

It is important to recognize that the term "flare" has been used imprecisely in the literature to describe a number of distinct processes associated with LHRH therapy. We here separate and define these as follows (Fig. 2): (1) "T flare" refers to the transient rise in serum T following LHRH agonist initiation; (2) " PSA flare" refers to a transient rise in serum PSA resulting from the transient rise in serum T; and (3) "disease flare" refers to evidence of disease progression during the transient rise in T.

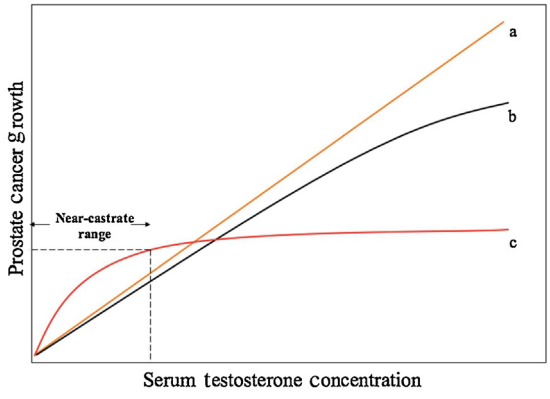

Fig. 1 – Saturation model as proposed by Morgentaler [1]. Lines a and b represent the traditionally understood growth of PCa in response to T. Curve c represents the current understanding of PCa growth in response to T—demonstrating no ongoing increase in prostate cancer growth in response to increasing T concentrations once the saturation point is reached. PCa = prostate cancer; T = testosterone.

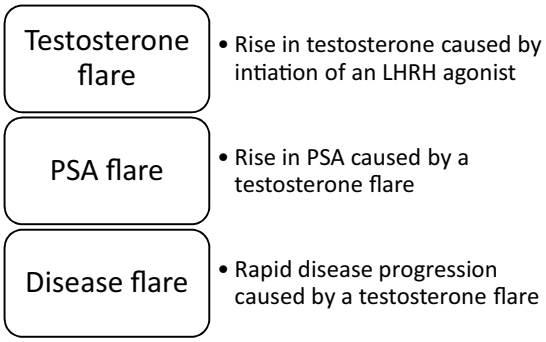

Fig. 2 – Suggested terminology in evaluating clinical response to LHRH agonist therapy. LHRH = luteinizing hormone–releasing hormone; PSA = prostate-specific antigen.

Please cite this article in press as: Krakowsky Y, Morgentaler A, Risk of Testosterone Flare in the Era of the Saturation Model: One More Historical Myth. Eur Urol Focus (2017), http://dx.doi.org/10.1016/j.euf.2017.06.008

2. Evidence acquisition

A narrative review was performed using an Ovid Medline database search to identify articles related to "testosterone flare," "disease flare," "PSA flare," or "prostate-specific antigen flare" associated with LHRH agonists. The literature review included papers published from May 1, 1980 through May 1, 2016 using search terms "luteinizing hormone releasing hormone" AND "agonist" OR "gonadotropin-releasing hormone" AND "agonist." Additional search terms included "prostate" "prostate cancer," "prostate carcinoma," AND "flare" OR "flare-up," as well as "LHRH agonist," "anti-androgen," "bicalutamide," "flutamide," "nilutamide," and "cyproterone acetate." Citations were checked for additional cross references

A separate OVID Medline database search was conducted to identify articles related to LHRH agonist and safety studies. This literature review included papers published until May 1, 2016 using search terms "luteinizing hormone releasing hormone agonist" OR "gonadotropin-releasing hormone" AND "prostate" AND "safety" OR "efficacy". Citations were checked for additional cross references.

Articles were included in the narrative review if they reported on disease flare or PSA flare in patients with PCa being treated with LHRH agonists. Studies that reported on LHRH agonist therapy without reference to PSA or disease flare were excluded.

3. Evidence synthesis

We identified a limited literature that investigated PSA changes or assessments of disease progression during the first 2–3 wk following LHRH agonist administration, corresponding to the period of T flare and its immediate aftermath.

Six studies were identified that reported PSA levels during the period of T Flare. Five randomized control trials (RCTs) and 17 observational studies were identified that reported disease flare during the period of T flare.

3.1. Results

3.1.1. PSA flare

Six studies reported PSA levels during T flare (Table 1 and Fig. 3). As expected, all showed more rapid PSA decline when LHRH agonists were combined with some form of AA treatment compared with LHRH agonist alone. With regard to PSA flare, however, five showed no significant PSA increase during T flare and one did. The trials are presented individually below.

Kuhn et al [2] randomized 36 men with metastatic PCa to buserelin versus buserelin with nilutamide. At baseline, mean age was 69.9 yr in the buserelin with nilutamide group (group 1) and it was 73.4 in the buserelin-alone group (group 2); mean PSA levels were 546 ng/ml (group 1) and 678 ng/ml (group 2). Mean prostatic acid phosphatase (PAP) levels were 13.9 μg/l (group 1) and 16.8 μg/l (group 2), and mean serum T 315 ng/dl (group 1) and 300 ng/dl (group 2). No significant increase in mean PSA was noted for men receiving buserelin alone despite a rise in serum T of approximately 100% over baseline. Once T levels declined to castrate levels by day 22, PSA and acid phosphatase concentrations also dropped substantially. Pain scores based on a visual analog scale were higher in the buserelin-alone group. No patient demonstrated disease flare.

Kotake et al [11] randomized 371 patients with advanced PCa to treatment with goserelin alone versus goserelin with an AA or estrogen. Mean age was 73.7 yr, mean PSA 188, and mean T 436 ng/dl. There were no significant differences in baseline characteristics across the study groups. On day 3, the goserelin-only group demonstrated a minor PSA increase of approximately 10%, not noted to be statistically significant compared with baseline. No patient demonstrated disease flare.

Noguchi et al [12] randomized 24 patients with untreated PCa to LHRH agonist versus LHRH agonist with flutamide. Mean age in the LHRH agonist group alone was 70 yr, mean PSA 135 ng/ml, and mean T 392 ng/dl. Mean PSA did not rise significantly above baseline. No patient demonstrated disease flare.

Table 1 – Studies evaluating PSA flare associated with LHRH agonist.

Study	Study type	*N*	Patient population	Mean baseline testosterone (ng/dl)	Mean baseline PSA (ng/ml)	PSA flare	Disease flare
Kuhn et al [2]	RCT	36	Untreated, metastatic disease	300	678	No	12/19 men with new or increased bone pain on a visual analog scale
Sasagawa et al [14]	Observational	16	Untreated, metastatic disease	535	202.7	Yes, but weak correlation to T changes	No
Kotake et al [11]	RCT	371	Untreated locally advanced or metastatic disease	436	188	No	No
Noguchi et al [12]	RCT	24	Untreated, diverse	390	135	No	No
Tsushima et al [13]	RCT	26	Untreated, diverse	400	379.6	No	No
Tomera et al [3]	RCT	242	Metastatic or PSA recurrence or neoadjuvant	454	7.9	No	No

LHRH = luteinizing hormone–releasing hormone; NR = not recorded; PSA = prostate-specific antigen; RCT = randomized control trial; T = testosterone.

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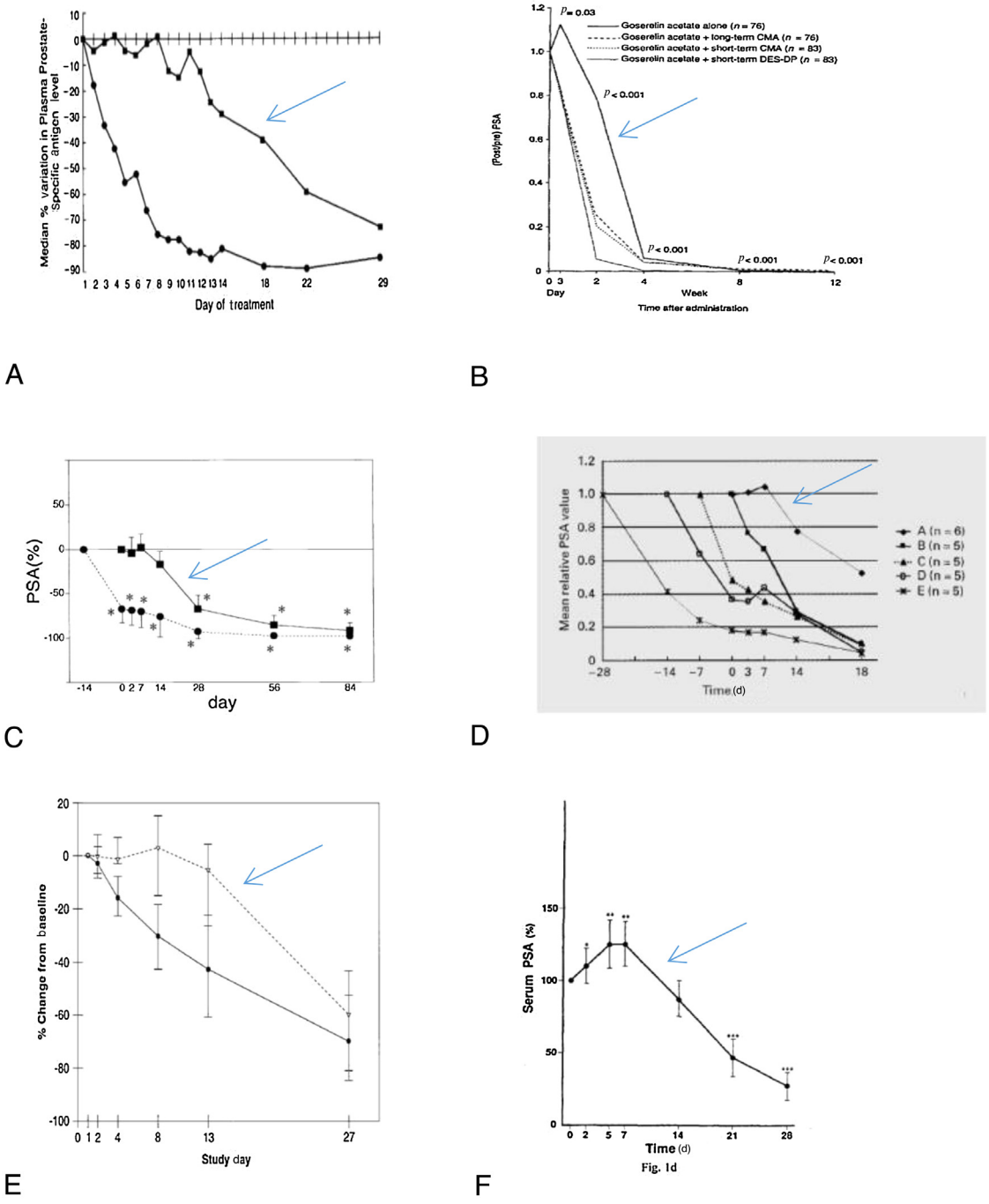

Fig. 3 – PSA response to LHRH agonist therapy without antiandrogen (arrow pointing to curves of LHRH agonist monotherapy). *Y* axis represents changes in PSA, *X* axis represents time from initiation of therapy. (A) Kuhn et al [2] demonstrating that PSA levels do not exceed baseline values after the initiation of an LHRH agonist. (B) Kotake et al [11] demonstrating a modest increase in PSA corresponding to T flare on day 3. While the increase is reported as statistically significant compared with the other groups, it is not significant compared with baseline PSA. (C) Noguchi et al [12] demonstrating no significant increase in PSA following the initiation of LHRH agonist alone starting at day 0. Square boxes represent patients who received LHRH agonist alone. (D) Tsushima et al [13] demonstrating a very modest and statistically insignificant increase in PSA at the time of T surge. No disease flare was noted in this study. (E) Tomera et al [3] demonstrating no significant PSA flare associated with the beginning LHRH alone. (F) Sasagawa et al [14] demonstrating a PSA flare in 16 patients with advanced metastatic disease treated with LHRH agonists only. No disease flare was seen. CMA = chlormadinone acetate; DES = diethylstilbestrol; DP = docetaxel and prednisolone; LHRH = luteinizing hormone–releasing hormone; PSA = prostate-specific antigen; T = testosterone.

Tsushima et al [13] randomized 26 patients with untreated PCa to receive LHRH agonist therapy alone or with the addition of flutamide, administered at various time intervals. The patient population included patients with both local and widely metastatic disease. Median age in the LHRH agonist monotherapy group was 73.5 yr, mean PSA 79.6 ng/ml, and mean T 500 ng/dl. In the LHRH agonist-alone group, a nonsignificant mean PSA increase of

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<5% above baseline was noted on day 7. No patient demonstrated disease flare.

Tomera et al [3] randomized 242 patients with advanced PCa to LHRH antagonist (aberelix) or to LHRH agonist with or without an AA. Mean age was 73 yr, mean PSA 7.9 ng/ml, and mean T 454 ng/dl. Mean PSA did not increase above baseline in the LHRH agonist group during the period of T flare, with a peak mean T concentration of 716 ng/dl. No patient demonstrated disease flare.

Sasagawa et al [14] treated 16 Japanese patients with documented bone metastases with leuprolide alone. No AA was given. Mean age was 72 yr, mean PSA 202 ng/ml, and mean T 535 ng/dl. Serum LH and T peaked at 2 d and then rapidly declined. A statistically significant rise in PSA and PAP was observed during T flare. Interestingly, changes in PSA did not correlate with changes in serum T. No patient demonstrated disease flare.

3.1.2. *Disease flare*

Five RCTs and 17 observational studies (Table 2) addressed disease flare associated with the initiation of LHRH agonist therapy.

The 17 observational studies primarily consisted of men with previously untreated metastatic PCa. Patients were symptomatic in most but not all cases. Study cohort sizes ranged from 12 to 118 patients, and LHRH agonist formulations included buserelin, goserelin, or leuprolide. Seven studies reported a transient increase in bone pain. There were two cases of spinal cord compression. The absence of a control group of untreated men in these studies confounds any attempt to draw conclusions as to how these results compare with those of untreated men. When reported, T flare is uniformly documented between 2 and 4 d after therapy with return of T concentrations to baseline or lower by 7 d.

In the RCTs, disease flare is generally defined as an increase in bone pain, urinary symptoms, or spinal cord compression. Most men in these trials had untreated metastatic disease at presentation. The size of the trials varies from 98 to 603 patients. Treatment formulations of LHRH agonists included goserelin, buserelin, or leuprolide. The use of those agents alone is compared with bilateral orchiectomy, diethylstilbestrol (DES), or coadministration with an AA. Three of these studies did not observe any disease flare in patients treated with LHRH agonists alone during the expected period of T flare. One reported a transient increase in pain in the "LHRH alone" arm. In addition, one RCT compared LHRH agonists with the addition of either flutamide or cyproterone acetate. Slightly greater bone pain was noted in the latter group. Unfortunately, the literature regarding disease flare does not consistently report the timing of disease flare; however, when reported, the timing of disease flare was consistently within the first 2 wk of LHRH agonist initiation.

Absent from the literature are RCTs of LHRH agonist treatment compared with no treatment. It is therefore impossible to determine whether early instances of increased bone pain or other indicators of disease progression in men receiving LHRH agonists represent the natural history of advanced disease or an adverse response to T flare. To date, there is a lack of high-level evidence comparing disease flare with LHRH agonists to the natural history of advanced PCa as most studies are observational. Although the evidence is inadequate to definitively conclude that AAs provide no benefit, the available evidence suggests that they have limited utility.

3.1.3. *Spinal cord compression*

It has routinely been taught for several decades that spinal cord compression due to vertebral collapse is a risk of T flare. Since the resulting paralysis that may occur represents the most dreaded potential complication of T flare, we specifically queried the literature to determine the basis for this concern.

In 1985, Waxman et al [15] published a brief report regarding 46 men who received LHRH agonists alone, 35 who received buserelin, and 11 who received decapeptyl. Baseline clinical values such as age, acid phosphatase, and T were not provided. They noted pain progression in 17 cases, becoming maximal at 36 h and easing by the end of the first treatment week. The method of assessing pain was not mentioned. They also reported one case of "tumor flare" in a patient whose initial presentation included bone pain and grade 4 weakness of the legs associated with thecal indentation in the lumber region on myelogram. Thirteen days following initiation of LHRH agonist treatment, the patient developed complete sphincter dysfunction and grade 3 weakness. A myelogram showed more prominent thecal compression. It should be noted that T concentrations should substantially be reduced by day 13.

In 1987, Ahmann et al [16] reported two cases of cord compression occurring within the 1 st week in their series of 46 patients with advanced PCa treated with goserelin. Both patients had extensive bony metastases at the time of presentation. Neither PSA nor acid phosphatase was reported. Median serum T at baseline was approximately 350 ng/dl, with 15 of 45 (33%) men having baseline serum T <300 ng/dl, including two with severe T deficiency with T <150 ng/dl. Baseline serum T concentrations of the two men with spinal compression were not provided. The authors acknowledge that it is impossible to determine whether these adverse events occurred due to spontaneous disease progression or T flare.

Peeling [17] reported on two related trials in one article: one was goserelin ($N = 176$) versus bilateral orchiectomy ($N = 182$), and the second was goserelin ($N = 124$) versus DES ($N = 126$). Subjective and objective responses were similar. Increased bone pain was noted in six of 176 men (3%) who received goserelin in the first trial and in five of 124 (4%) in the second trial, compared with no reports of increased bone pain with orchiectomy or DES. No change in treatment was required for those reporting increased bone pain. In the first trial, there was one case of spinal cord compression in the goserelin arm and one in the orchiectomy arm. In the second trial, there was also one case of spinal cord compression in the goserelin arm and one in the DES arm.

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Table 2 – Disease flare in advanced metastatic prostate cancer studies.

Author	Study type	Agent	*N*	Patient population	Mean baseline T (ng/dl)	T flare timing	Disease flare	Disease flare timing
Peeling [17]	RCT	Goserelin versus orchiectomy versus DES	358	Untreated metastatic	NR	NR	3% bone pain (LHRH-A vs orchiectomy) 4% bone pain (LHRH-A vs DES)	NR
Lunglmayr [29]	RCT	Goserelin ± flutamide	586	Untreated metastatic	NR	NR	None	None
Crawford et al [30]	RCT	Leuprolide ± flutamide	603	Untreated metastatic	NR	NR	None	None
Ferrari et al [31]	RCT	Buserelin ± CPA versus buserelin ± flutamide	122	Untreated metastatic	NR	NR	Three patients with transient bone pain in the CPA group	NR
The Leuprolide Study Group [32]	RCT	Leuprolide versus DES	98	Metastatic disease	NR	NR	None	None
Ahmann et al [16]	Observational	Goserelin	46	Local and metastatic	330	Day 2	17% increase in bone pain, two patients with cord compression	Within 1 st week
Waxman et al [15]	Observational	Buserelin	12	Untreated, mainly metastatic	46	Day 2	None	None
Presant et al [33]	Observational	Buserelin	28	Untreated, locally advanced, and metastatic	NR	NR	One patient with “flare of symptoms”	NR
Waxman et al [34]	Observational	Buserelin or decapeptyl	46	Symptomatic locally advanced or metastatic	NR	NR	One patient with cord compression, 17 bone pain, one AKI	Cord compression at 13 d, pain at 36 h
Holdaway et al [35]	Observational	Goserelin	38	Untreated, symptomatic metastatic disease	NR	NR	11% increased pain	NR
Sharifi et al [36]	Observational	Leuprolide	94	Metastatic	406	Day 4	17% new pain, 4% worsening of pain, 2% LUTS	Within 14 d
Smith [37]	Observational	Leuprolide versus estrogen versus orchiectomy	118	Symptomatic metastatic disease	360	Day 4	9% transient increase in bone pain	NR
Murphy et al [38]	Observational	Goserelin	27	Locally advanced and metastatic	NR	Day 2	Three patients with worsening of pain, one with urinary obstruction	Within first 2 wk
Sharifi et al [39]	Observational	Leuprolide	49	Metastatic disease	424	Day 1	One patient with bone pain	Within first 2 wk
Crawford et al [40]	Observational	Leuprolide	111	Diverse	360	Day 2	None	None
Braeckman and Michielsen [41]	Observational	Leuprolide	243	Diverse	260	NR	None	None
Tunn and Wiedey [42]	Observational	Leuprolide	178	Diverse	NR	NR	None	None
Marberger et al [10]	Observational	Leuprolide	160	Asymptomatic	412	Day 3	None	None
Chu et al [43]	Observational	Leuprolide	117	Diverse	NR	Day 2	None	None
Perez-Marreno et al [44]	Observational	Leuprolide	117	Locally advanced or metastatic	NR	Day 3	None	None
Suzuki et al [45]	Observational	Leuprolide	162	Diverse	NR	NR	None	None
Oh et al [46]	Retrospective	Leuprolide	1566	Metastatic	NR	NR	None	None

CPA = cyproterone acetate; DES = diethylstilbestrol; LHRH = luteinizing hormone–releasing hormone; LUTS = lower urinary tract symptoms; NR = not recorded; RCT = randomized control trial.

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3.2. Discussion

The introduction of LHRH agonist therapy in the 1980s as a form of "medical castration" was regarded as a major advance over the standard practice of performing surgical castration, that is, bilateral orchiectomy, in men with advanced PCa, as it removed the psychological stigma of removing a man's testicles. It was also regarded as preferable to treatment with DES, which at that time was associated with reports of unacceptably high cardiovascular risks [18]. However, one major concern with LHRH agonist therapy was T flare.

In 1981, Fowler and Whitmore [19] reported that 45 of 52 men with metastatic PCa treated with T injections experienced an "unfavorable" outcome within 1 mo. These results fueled the belief that T administration in men with PCa was nearly always associated with rapid PCa growth, spawning phrases such as "like pouring gasoline on a fire." It is understandable in that historical context that T flare would be assumed to be the cause of any adverse event that occurred soon after administration of an LHRH agonist. Twenty-five years later, it was recognized that the group reported by Fowler and Whitmore [19] were all androgen deprived with the exception of four men, and those hormonally intact men did well, with one of them receiving daily T injections for 355 d without apparent ill effect, consistent with the saturation model [1].

The general belief in the dangers of T flare is illustrated by publication in 1990 of two case reports with the title "Sudden death due to disease flare with luteinizing hormone-releasing hormone agonist therapy for carcinoma of the prostate." This report describes one individual with metastatic PCa who died of unknown causes 5 d after administration of an LHRH agonist and another who died at 3 wk from respiratory arrest, when his serum T concentration would already have approached castrate levels [20]. Clearly, it is impossible to attribute causality to these cases, since death is a not unexpected outcome in advanced PCa. Fears regarding T flare soon led to the routine addition of AAs for the initial treatment period, a practice that continues to this day [21].

The relatively new concept that androgens have a limited capacity to stimulate PCa growth has particular relevance to T flare concerns. Indeed, our critical review of the evidence fails to support the long-assumed belief that T flare causes PCa progression or is associated with significant risks. In five of six studies that measured PSA during the T flare period, there was no significant rise in PSA above baseline. The one study that showed a rise in PSA involved only 16 men, and there was no correlation between the rise in serum PSA and the rise in serum T [14]. This may have been the result of participation by several individuals whose baseline T was below the saturation point at baseline, as these men are still vulnerable to additional androgenic stimulation of their PCa. Individual baseline T concentrations were not provided to assess this possibility.

We found no compelling evidence that T flare was associated with disease progression. Most studies reported no disease flare at all during the interval of elevated T. A small number reported increased bone pain within the first few weeks compared with treatments such as LHRH agonists with AAs [2] or orchiectomy or DES [17]. Since there is a delay of 7–8 d before serum T declines substantially with LHRH agonists, the explanation for relatively greater pain compared with other treatments may simply reflect the difference between immediate versus delayed decline in T concentrations or activity rather than symptoms related to increased T with flare. Bone pain from metastases was a common initial presenting complaint for men with PCa in the 1980s and 1990s when these studies were performed, and its presence in these men should be regarded as consistent with the natural history of PCa rather than as a de novo adverse effect caused by T flare.

Finally, it is striking to review the evidence regarding spinal compression with its attendant risk of paralysis as the most feared risk of T flare. In these series, spinal compression rates were equal in men receiving LHRH agonists alone compared with other treatments that caused immediate declines in serum T, such as orchiectomy or DES administration. The overall rate of this complication was approximately 1% across all reviewed series. In randomized trials, the rates of spinal compression were similar for LHRH agonists alone compared with other treatments that immediately lowered serum T, that is, bilateral orchiectomy or DES administration. Importantly, these cases reveal that spinal cord compression occurs not only due to the natural history of advanced disease, but also in the setting of castrate serum T concentrations, and is therefore not at all specific to T flare.

These results are consistent with a number of lines of evidence indicating that higher endogenous serum T or T therapy itself are not nearly as risky for PCa as once believed. High endogenous serum T in population studies appears to confer no increased risk of developing PCa [22]. A meta-analysis of 22 studies showed that rates of PCa are not higher in men receiving T than that in men receiving placebo [23]. Cohorts of men who received T therapy after definitive treatment with radical prostatectomy, brachytherapy, or radiation therapy demonstrated very low rates of PCa recurrence [24–26]. Finally, progression rates were no greater for 28 men on active surveillance who received T therapy compared with 96 similar men who did not receive T therapy with a mean follow-up of 3 yr [27]. However, to date, there is no literature exploring the safety of T Therapy in men with advanced PCa.

In a previous review, Vis et al [28] also noted only weak evidence supporting disease progression with T flare, mainly in the form of anecdotal case reports where it is impossible to distinguish between the effects of a treatment and the natural history of advanced PCa. They argued for abandoning coadministration of AAs due to the lack of evidence supporting T flare as a precipitator of disease progression. While there is no definitive published evidence to support that notion, we support that recommendation with one important exception. We note that men with serum T concentrations well below the saturation point still have capacity for appreciable androgenic stimulation of PCa growth, and we therefore recommend that prior to

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administration of LHRH agonists, men with extensive vertebral metastases have their serum T measured, and that AAs are offered if serum T is well below the saturation point of 250 ng/dl or 8.7 nmol/l.

4. Conclusions

We find no compelling evidence to support the long-held belief that T flare is associated with increased PCa risk, including spinal cord compression, even in men with far advanced disease. These results are consistent with the saturation model. In light of these findings, we question the value of administration of AAs together with the initiation of LHRH agonists. One special case where AAs should still be considered is a patient with extensive vertebral metastases and serum T well below the saturation point. While there is no high-level evidence to support the practice, we think that it is reasonable to measure serum T prior to administration of LHRH agonists in men with extensive vertebral metastases.

Author contributions: Abraham Morgentaler had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Morgentaler, Krakowsky.
Acquisition of data: Morgentaler, Krakowsky.
Analysis and interpretation of data: Morgentaler, Krakowsky.
Drafting of the manuscript: Morgentaler, Krakowsky.
Critical revision of the manuscript for important intellectual content: Morgentaler, Krakowsky.
Statistical analysis: Morgentaler, Krakowsky.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Morgentaler.
Other: None.

Financial disclosures: Abraham Morgentaler certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Abraham Morgentaler: consultancies/ad boards: Besins Healthcare (12/31/2015), Endo Pharmaceuticals (12/31/2015), Pfizer Inc. (12/31/2015), Repros Therapeutics (12/31/2015), AbbVie Inc. (6/16/2016), Bayer Pharma (09/22/2016), BioTE (10/01/2016), Aytu BioScience, Inc. (11/02/2016), Tolmar Pharmaceuticals Inc. (11/03/2016), American Medical Systems (12/31/2016).

Funding/Support and role of the sponsor: None.

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Please cite this article in press as: Krakowsky Y, Morgentaler A, Risk of Testosterone Flare in the Era of the Saturation Model: One More Historical Myth. Eur Urol Focus (2017), http://dx.doi.org/10.1016/j.euf.2017.06.008