Effect of dutasteride in men receiving intermittent androgen ablation therapy: The AVIAS trial

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Abstract

Introduction: We studied the effect of dutasteride on the length of the off-treatment period in prostate cancer patients on intermittent androgen deprivation (IAD) therapy.

Methods: We conducted a randomized, placebo-controlled Phase II trial in men with localized prostate cancer and a rising prostate-specific antigen (PSA) level post-primary treatment. Patients were randomized to dutasteride (0.5 mg/day) or placebo. All patients received androgen deprivation therapy (ADT), which was stopped at month 9 if the PSA level was <1.0 ng/mL. ADT was resumed when PSA increased to ≥5.0 ng/mL. End points included time off treatment, PSA nadir after 9 months of ADT, serum testosterone and dihydrotestosterone levels, and time to castrate-resistant prostate cancer (rising PSA while testosterone levels remain <50 ng/mL).

Results: There were 87 evaluable patients: 49 dutasteride, 38 placebo. In total, 80 patients completed one treatment cycle: 45 dutasteride, 35 placebo. The median time off treatment for patients reaching ≥5 ng/mL was 18.6 and 16.7 months for dutasteride and placebo, respectively (p = 0.7600). The median PSA nadir at 9 months was 0.1 and 0.075 ng/mL, respectively (p = 0.4486). There were no cases of androgen-independent prostate cancer. Our study limitations include its short duration with only one treatment cycle evaluated.

Conclusions: This small-scale Phase II randomized controlled trial showed no benefit to the addition of dutasteride to an IAD regimen.

Introduction

Androgen deprivation therapy (ADT), a mainstay of prostate cancer treatment,[1] has a number of unwanted adverse effects, including erectile dysfunction, hot flushes, anemia, muscle atrophy, obesity, gynaecomastia, mood changes, depression and alterations in lipid metabolism.[2] The development of castrate-resistant prostate growth is inevitable in most patients. Intermittent ADT was first introduced by Klotz and associates in 1986 to reduce the morbidity associated with ADT.[3] Since then, about 20 phase II and 4 phase III trials have demonstrated the safety and benefit of intermittent therapy (recently summarized in an overview by Abrahamsson[4]). Recently, a large-scale trial in non-metastatic disease (PR7) demonstrated conclusively the non-inferiority of intermittent therapy with respect to overall survival.[5] A similar trial in metastatic disease (SWOG 8394) was inconclusive in terms of non-inferiority, but did not show inferiority.[6] Intermittent androgen deprivation (IAD) is widely used, particularly for biochemical failure.[7] All IAD studies utilize PSA recovery as a trigger for re-treatment, with a PSA threshold of between 5 and 20.[4]

5-alpha reductase converts testosterone to dihydrotestosterone (DHT). Dutasteride inhibits 5AR types 1 and 2.[8] Two studies have shown that 5-alpha reductase inhibitors (5ARIs) reduce the risk of prostate cancer.[9,10] In men with benign prostatic hyperplasia (BPH), 5ARIs reduce serum prostate-specific antigen (PSA) levels by 50% to 66%.[11,12]

In a phase 2 study with historic controls, 5ARIs prolonged the off-treatment interval in men on IAD.[13] It is unknown whether this is due to inhibition of proliferation of prostate cancer cells or merely inhibition of PSA secretion. Recent evidence suggests that testosterone may induce differentiation and cell cycle arrest in prostate cancer (in contrast to the mitogenic effect of DHT).[14] Consequently, a 5ARI that raises testosterone and reduces levels of nuclear DHT could provide a useful adjunct to IAD.

The objective of the current study was to determine whether the length of the off-treatment period is prolonged by dutasteride in men on IAD.

Methods

Study design and participants

Men with localized prostate cancer with a rising PSA post-primary treatment (radical prostatectomy or radiotherapy) and starting on IAD were enrolled in this multicentre, phase II randomized, double-blind placebo-controlled study. The study was conducted in 12 centres in Canada and the USA between 2007 and 2013. The inclusion and exclusion criteria are shown in Table 1. Patients were randomized to dutasteride 0.5 mg daily or placebo, administered throughout the course of the study. All patients received 9 months of ADT consisting of a lutenizing hormone-releasing hormone (LHRH) agonist given as three 3-month depots and bicalutamide 50 mg once daily.

Serum PSA and testosterone levels were monitored at 3-month intervals. At month 9, if the serum PSA was <1.0 ng/mL, ADT was interrupted. Serum PSA and testosterone were then monitored monthly. When the serum PSA increased to ≥5.0 ng/mL, ADT was resumed. At month 9, if the serum PSA was ≥1.0 ng/mL, the patient was taken off-study but continued to receive ADT. When the PSA increased on 3 successive determinations above the nadir while serum testosterone <50 ng/mL, patients were considered castrate resistant. One full treatment cycle was defined as 9 months of ADT plus time off treatment, defined as either PSA >5.0 ng/mL or an off-treatment interval >24 months.

The study terminated when the last randomized patient reached a PSA of 5.0 ng/mL ***or*** had an off-treatment interval of 24 months. All patients provided written informed consent to participate in the study. The study was approved by institutional review boards from each participating institution.

Study endpoints

The primary study endpoint was time to PSA ≥5.0 ng/mL in the off-treatment interval, which was measured from the time of cessation of ADT. Secondary endpoints included: PSA nadir at the end of 9 months of ADT; serum testosterone and DHT levels achieved during IAD; and time to castrate-resistant prostate cancer. The PSA threshold which defined the end of the off-treatment interval was not individualized according to the allocation cohort. Although the effect of dutasteride on PSA in men with BPH is well-known, the effect on PSA in men with prostate cancer recovering from a cycle of ADT is unknown. To avoid bias, we therefore used the same PSA threshold (≥5.0 ng/mL) for both groups.

Assessments

Physical exam including digital rectal examination (DRE) and qualitative gynaecomastia evaluation; serum PSA and testosterone measurements were conducted at screening, at months 1, 3, 6 and 9 during ADT treatment. Serum DHT determinations were completed at screening and month 6. A bone scan was performed within 12 months of the screening visit. During the off-treatment phase, PSA, testosterone, and DHT were measured monthly.

Statistical analysis

The null hypothesis of this study was that the addition of dutasteride would not lengthen the duration of the off-treatment interval by more than 33%. We assumed that the median duration of the off-treatment interval in the placebo group was 9 months. An enrolment of approximately 44 subjects per treatment group would provide 90% overall power to detect a 33% increase in duration of the off-treatment interval of the 0.5 mg dutasteride treatment group versus placebo with type I error of 0.05. The assumed withdrawal rate after 1 year was 15%; therefore, 50 patients per group were required.

To compare the homogeneity of dutasteride and placebo treatment arms, Wilcoxon rank-sum test and Fisher exact test were applied for continuous variables and categorical variables. A general linear mixed model was conducted on the following comparisons between treatment arms (fixed effect) with individual-specific random effect: (a) duration of off-treatment period; (b) PSA nadir after 9 months of ADT; and (c) time to castrate-resistant prostate cancer. The least squares mean (LSM) with standard error (SE) was also estimated in each treatment group from the model. To search for significant treatment effect on post-baseline serum PSA, testosterone and DHT levels over time, fixed effects included PSA at baseline, treatment, and time (in months). The interaction term between treatment and time was also tested for significance. Natural log-transformation was applied as appropriate for normalizing the distribution. All analyses were conducted using Statistical Analysis Software (SAS version 9.3 for Windows, SAS Institute, Cary, NC). PROC MIXED procedure in SAS was used for the modelling. Bonferroni adjusted p value < 0.013 was considered statistically significant for controlling multiple testing.

Results

A total of 96 patients were enrolled in the study. Of these, 5 were not randomized, which brings us to an intention-to-treat total population of 91 patients.

Of these 91 patients, 1 patient did not complete the 9-month visit, 1 patient had a PSA >1.0 ng/mL at month

9 and discontinued the study, and 2 patients discontinued prior to month 9 due to the withdrawal of consent in 1 and an adverse event in the other. The remaining 87 patients were categorized as the evaluable population (Fig. 1).

We noted the baseline characteristics of remaining 87 patients (Table 1). Treatment groups were well-balanced. The homogeneity of dutasteride and placebo groups was consistent ($p > 0.05$) for all baseline demographics. We found that 23% of all patients had prior ADT (in all cases at least 12 months prior). We also found that 88% of patients had been treated with radiotherapy and 12% with radical prostatectomy.

In total, 80 patients completed 1 treatment cycle (defined as a PSA ≥5 ng/mL off treatment, or an off-treatment interval of >24 months) (Table 2). The median time off treatment was shorter for dutasteride-treated patients (19.8 vs. 21.3 months), but the difference was not significant ($p = 0.42$). The LSM (SE) was 23.0 months (2.1) in the dutasteride group and 25.7 months (2.4) in the placebo group, respectively. For the 57 patients who reached a PSA value ≥5 ng/mL during the off-treatment period, there was no significant difference in the duration off treatment (median interval in the dutasteride vs. placebo groups, 18.6 vs. 16.7 months; $p = 0.76$). The LSM (SE) was 20.7 months (1.8) in the dutasteride group and 19.8 months (2.3) in the placebo group, respectively.

No statistical significance was reported for the difference in PSA nadir between groups ($p = 0.45$; LSM ± SE was 0.095 ± 0.012 in dutasteride and 0.084 ± 0.014 in placebo). We also noted the mean serum PSA, testosterone, and DHT levels during the off-treatment period (Fig. 2). Significant increasing time trends were found for PSA post-baseline values ($p < 0.0001$) and for testosterone ($p < 0.0001$) after adjusting for significant baseline records ($p = 0.007$ and $p < 0.0001$ for PSA and testosterone at baseline, respectively). Patients treated with dutasteride had a more rapid recovery of PSA and testosterone in the off-treatment interval compared to placebo ($p < 0.0001$). There were no significant time trends for post-baseline DHT levels ($p = 0.17$), and no significant treatment effect ($p = 0.21$). Of the 80 patients completing 1 treatment cycle, there were no cases of androgen-independent prostate cancer.

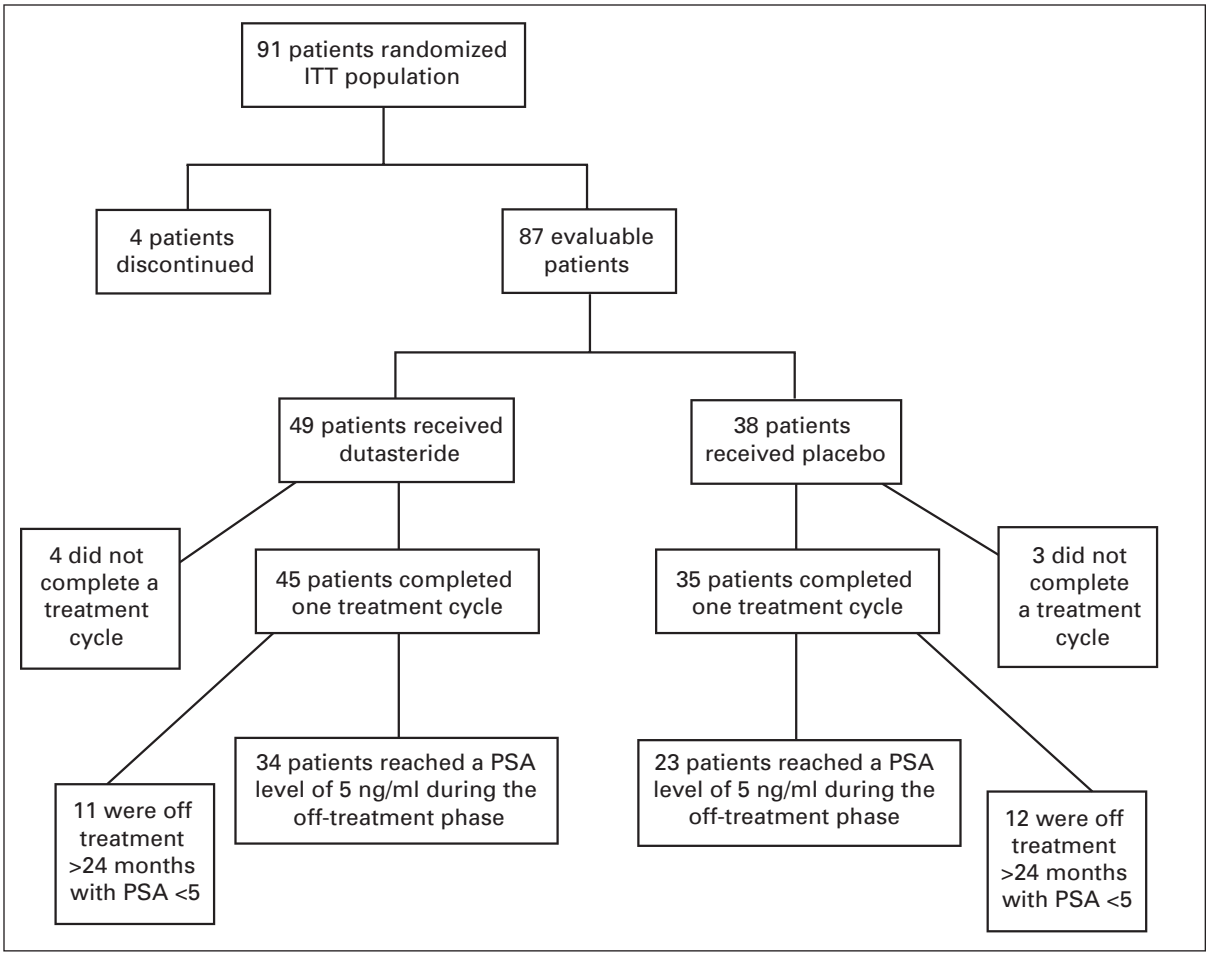

Fig. 1. Consort flow chart showing patient disposition.

Table 1. Baseline patient characteristics

	Total (n = 87)	Dutasteride (n = 49)	Placebo (n = 38)
Age (years)			
Median (interquartile)	71.0	72.6	69.4
Minimum, maximum	59, 88	59, 81	59, 88
Gleason score at baseline			
≤6	37 (37%)	17 (37%)	14 (37%)
7	42 (50%)	22 (48%)	20 (53%)
8	9 (11%)	6 (13%)	3 (8%)
9	2 (2%)	1 (2%)	1 (3%)
PSA at baseline (ng/mL)			
Median	5.1	5.6	5.1
Minimum, maximum	2.0, 75.1	2.3, 75.1	2.0, 24.9
ADT >12 months previously			
No	63 (77%)	37 (80%)	26 (72%)
Yes	19 (23%)	9 (20%)	10 (28%)
Prostate radiotherapy			
No	9 (12%)	7 (17%)	2 (6%)
Yes	65 (88%)	34 (83%)	31 (94%)

PSA: prostate-specific antigen; ADT: androgen deprivation therapy.

Table 2. Time off treatment for patient groups

	Time of off-treatment period (months)		
	Total	Dutasteride	Placebo
Patients completing 1 treatment cycle*			
No.	80	45	35
Mean (SD)	25.3 (14.8)	24.2 (13.7)	26.6 (16.2)
Median (interquartile)	19.9 (14, 35)	19.8 (14, 34)	21.3 (14, 39)
Minimum, maximum	5, 64	6, 55	5, 64
Patients reaching PSA values ≥5 ng/mL during off-treatment period			
No.	57	34	23
Mean (SD)	20.4 (10.7)	20.7 (10.5)	19.8 (11.3)
Median (interquartile)	18.3 (12, 27)	18.6 (13, 28)	16.7 (9, 27)
Minimum, maximum	5, 46	6, 46	5, 42
PSA nadir at month 9 (ng/mL)			
No.	87	49	38
Mean (SD)	0.10 (0.10)	0.10 (0.11)	0.09 (0.09)
Median (interquartile)	0.10 (0.03, 0.10)	0.10 (0.03, 0.10)	0.07 (0.03, 0.10)
Minimum, maximum	0, 0.51	0, 0.48	0.01, 0.51

*Either PSA ≥5 ng/mL or 24 months off treatment.

Discussion

There was no significant difference in the duration of the off-treatment interval between dutasteride and placebo. The median time off treatment of the dustasteride and the placebo groups was 19.8 and 21.3 months, respectively. In the 57 patients whose PSA reached >5.0 ng/mL prior to 24 months off treatment, the off-treatment interval was 18.6 and 16.7 months in the dutasteride and placebo groups, respectively. This was an 11% difference, and not statistically significant. In contrast, a retrospective analysis of 101 patients on IAD reported by Scholz and colleagues showed that finasteride increased the time off treatment from 15 to 31 months.[13] This study involved a different drug (finasteride), and different criteria for initiating and discontinuing treatment. Finasteride was administered in the off-treatment interval only, in contrast to this present study. The PSA threshold for re-treatment was reduced to 2.5 ng/mL in the finasteride group and 5.0 in the historic control group. In the current study, the time off treatment was defined as the time from stopping ADT until the PSA level increased to ≥5.0 ng/mL; no distinction was made between patients treated with dutasteride or placebo.

The lack of improvement in off-treatment time in the current study raises uncertainty regarding the benefit of 5ARIs in men with recovering testosterone and PSA after ADT. This uncertainty may be due to the "unmasking" of PSA secretion by 5ARI-resistant prostate cancer cells in the setting of IAD, in contrast to BPH. The PSA kinetics might be accelerated by the presence of 5ARI-resistant prostate cancer cells. It is also possible that 5ARIs exert a deleterious effect on prostate cancer in this situation, promoting more rapid recovery of PSA than expected. Controversy exists with respect to the induction of high-grade cancer by 5ARIs, since both the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial showed a small increase in Gleason ≥8 in the 5ARI arm.[9,10] Although the FDA published a subsequent warning,[15] investigators believe that the increase reflected ascertainment bias.[16] Prostate cancer mortality from high-grade disease in the PCPT was the same in both groups, suggesting that the increase was artifactual.[17]

The absence of a difference in the 9-month PSA nadir suggests that the benefit of 5ARI during the ADT induction period is minimal. Patients treated with dutasteride had a higher increase of PSA and testosterone during the off-treatment interval. There was no difference in serum DHT levels.

Our study has its limitations. Only 1 treatment cycle was evaluated and the follow-up was short. Examining the effects of dutasteride over a longer time period would clarify the impact of 5ARIs on subsequent cycle length and time to castration resistance. The study was underpowered to show a modest difference in the off-treatment interval.

Conclusion

Dutasteride had a no significant effect on the duration of the off-treatment interval when added to an IAD regimen in men with localized prostate cancer treated with ADT.

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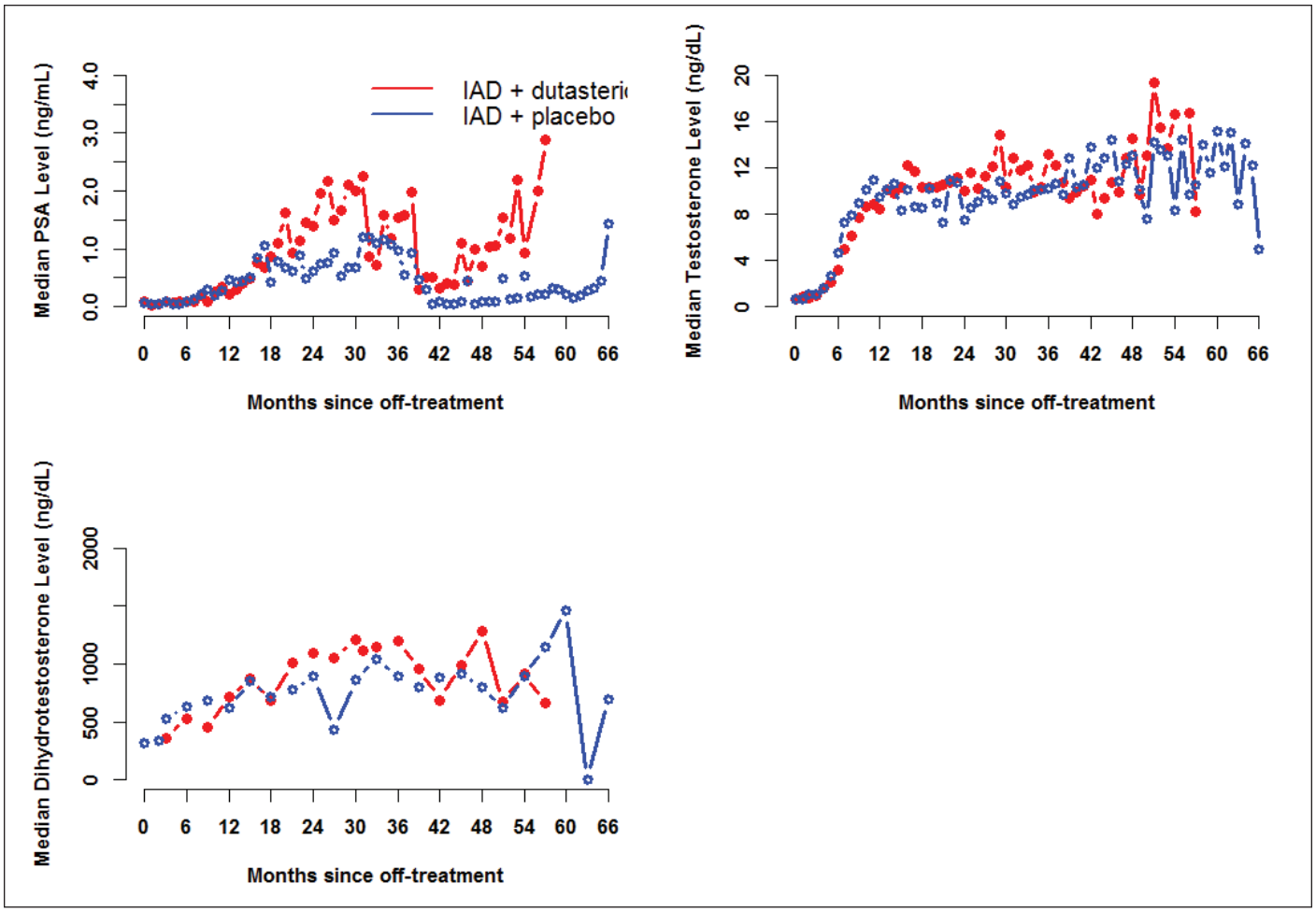

Fig. 2. Median levels during first off-treatment period of: (a) serum prostate-specific antigen (PSA); (b) testosterone; and (c) dihydrotestosterone (DHT).

Competing interests: Dr. Nabid, Dr. Higano, Dr. Ryanm, Dr. Kebabdjian and Dr. Chin all declare no competing financial or personal interests. Dr. Klotz has received clinical research funding from Bayer/Aigeta, Ferring, Abbott, GSK, and EMD Serono. He is on the Advisory boards for and has received speaking honoraria from Dendreon, Amgen, Janssen, Ferring, GSK and Profound. He has also received speaking honoraria from Sanofi-Aventis and Merck.

Notes: Trial registry name: Comparing 0.5 mg Dutasteride vs Placebo Daily in Men Receiving Androgen Ablation Therapy for Prostate Cancer; Trial registry URL: www.clinicaltrials.gov; Trial registration no: NCT00553878

This paper has been peer-reviewed.

References

1. Mottet N, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. http://www.uroweb.org/gls/pdf/09%20Prostate%20Cancer_LRLV2.pdf. Accessed November 4, 2014.
2. Kozlowski J, Grayhack J. *Carcinoma of the Prostate.* 2nd ed, Chicago: Mosby Year Book; 1991.
3. Klotz L, Herr H, Morse M, et al. Intermittent endocrine therapy for advanced prostate cancer. *Cancer* 1986;8:2546. http://dx.doi.org/10.1002/1097-0142(19861201)58:11<2546::AID-CNCR2820581131>3.0.CO;2-N
4. Abrahamsson PA. Potential benefits of intermittent androgen suppression therapy in the treatment of prostate cancer: A systematic review of the literature. *Eur Urol* 2010;7:49. http://dx.doi.org/10.1016/j.eururo.2009.07.049
5. Crook JM, O'Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med* 2012;367:895-903. http://dx.doi.org/10.1056/NEJMoa1201546
6. Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med* 2013;368:1314-25. http://dx.doi.org/10.1056/NEJMoa1212299
7. Klotz LH. Intermittent vs continuous androgen deprivation therapy in advanced prostate cancer. *Curr Urol Rep* 2013;14:159-67. http://dx.doi.org/10.1007/s11934-013-0325-x
8. Oelke M, Bachmann A, Descazeaud A, et al. Guidelines on male lower urinary tract symptoms (LUTS), incl, benign prostatic obstruction (BPO). European Association of Urology 2013. http://www.uroweb.org/gls/pdf/13_Male_LUTS_LR.pdf. Accessed November 4, 2014.
9. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349:215-24. http://dx.doi.org/10.1056/NEJMoa030660
10. Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 2010;362:1192-202. http://dx.doi.org/10.1056/NEJMoa0908127
11. Guess HA, Gormley GJ, Stoner E, et al. The effect of finasteride on prostate-specific antigen: Review of available data. *J Urol* 1996;155:3-9. http://dx.doi.org/10.1016/S0022-5347(01)66524-8
12. Marks LS, Andriole GL, Fitzpatrick JM, et al. The interpretation of serum prostate specific antigen in men receiving 5 alpha reductase inhibitors: A review and clinical recommendations. *J Urol* 2006;176:868-74. http://dx.doi.org/10.1016/j.juro.2006.04.024
13. Scholz MC, Jennrich RI, Strum SB, et al. Intermittent use of testosterone inactivating pharmaceuticals using finasteride prolongs the time off period. *J Urol* 2006;175:1673-8. http://dx.doi.org/10.1016/S0022-5347(05)00975-4

14. Dadras SS, Cai X, Abasolo I, et al. Inhibition of 5alpha-reductase in rat prostate reveals differential regulation of androgen-response gene expression by testosterone and dihydrotestosterone. *Gene Expr* 2001;9:183-94.
15. Theoret MR, Ning YM, Zhang JJ, et al. The risks and benefits of 5α-reductase inhibitors for prostate-cancer prevention. *N Engl J Med* 2011;365:97-9. http://dx.doi.org/10.1056/NEJMp1106783
16. Lucia MS, Epstein JI, Goodman PJ, et al. Finasteride and high-grade prostate cancer in the Prostate Cancer Prevention Trial. *J Natl Cancer Inst* 2007;99:1375-83. http://dx.doi.org/10.1093/jnci/djm117
17. Thompson IM Jr, Goodman PJ, Tangen CM, et al. Long-term survival of participants in the Prostate Cancer Prevention Trial. *N Engl J Med* 2013;369:603-10. http://dx.doi.org/10.1056/NEJMoa1215932

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