THE IMPORTANCE OF 5ALPHA REDUCTASE (5AR) INHIBITORS
(Despite the FDA's contrary conclusion)

Compiled by Charles (Chuck) Maack – Prostate Cancer Advocate/Activist

DISCLAIMER: Please recognize that I am not a Medical Doctor. I have been an avid student researching and studying prostate cancer as a survivor and continuing patient since 1992. I have dedicated my retirement years to continued research and study in order to serve as an advocate for prostate cancer awareness, and, from a activist patient's viewpoint, to voluntarily help patients, caregivers, and others interested develop an understanding of prostate cancer, its treatment options, and the treatment of the side effects that often accompany treatment. There is absolutely no charge for my mentoring – I provide this free service as one who has been there and hoping to make your journey one with better understanding and knowledge than was available to me when I was diagnosed so many years ago. Readers of this paper must understand that the comments or recommendations I make are not intended to be the procedure to blindly follow; rather, they are to be reviewed as my opinion, then used for further personal research, study, and subsequent discussion with the medical professional/physician providing your prostate cancer care.

Read the below information to the very end and learn the importance of 5AR inhibitors, and in particular, dutasteride/Avodart. It is so obvious that physicians are not taking the valuable time to better recognize this importance.

Regarding the Prostate Cancer Prevention Trial (PCPT) to determine the use of 5Alpha Reductase (5AR) inhibitors to prevent prostate cancer:

Overall survival among participants in the Prostate Cancer Prevention Trial

(Regarding finasteride for PC prevention)

http://tinyurl.com/9wfrotj

OF NOTE IS THE CONCLUSION:

***"With follow-up of 18 years, finasteride administration for 7-years does not appear to affect mortality but significantly reduces the risk of a … diagnosis** [of prostate cancer]."*

More here wherein is a reasonable explanation of why high grade PC may be found during biopsy following the prescribing of finasteride/Proscar or dutasteride/Avodart (not because "caused" by these drugs, but as the result of their shrinking gland size):

http://prostatecancerinfolink.net/risk-prevention/prevention-prostate-cancer/PCPT/

From Medical Oncologist Mark Scholz, specializing specifically in research and treatment of recurring and advanced prostate cancer:

http://prostatesnatchers.blogspot.com/2014/10/avodart-proscar.html

You should view this "blog" by Medical Oncologist Charles E. "Snuffy" Myers regarding where Avodart could be important as a monotherapy when a patient experiences PSA elevation post-surgical removal as evidence of Prostate Cancer recurrence. According to Dr. Myers, Avodart monotherapy could delay cancer progression as well as avoid the many side effects that can accompany, for example, salvage radiation, or even the prescribing of androgen deprivation medications (LHRH agonists, GnRH antagonist, antiandrogens): http://tinyurl.com/owtlsss

From ASCO and AUA's February 2009 Guideline on 5-alpha Reductase Inhibitors for Prostate Cancer Prevention:

KEY MESSAGES
• A class of drugs called 5-alpha reductase inhibitors (5-ARIs) may lower your risk of developing prostate cancer.
• Talk with your doctor about your risk of developing prostate cancer and whether you should be screened for prostate cancer.
• Talk with your doctor about the benefits and risks of taking a 5-ARI to lower your risk of prostate cancer.

"A somewhat confusing result of the PCPT showed that a higher number of men in the study who took finasteride were found to have high-grade prostate cancer,

compared with men who received a placebo (inactive substance). Doctors are unsure if finasteride caused this. ***MORE RECENT STUDIES SUGGEST THAT 5-ARIs DO NOT ACTUALLY INCREASE THE RISK OF DEVELOPING HIGHGRADE PROSTATE CANCER, BUT RATHER INCREASE THE ABILITY OF THE PSA TEST TO FIND HIGH-GRADE CANCERS THAT ARE ALREADY THERE."***

That was MY high-lighting of that last sentence. I believe a miss-wording occurred and that rather than "increase the ability of the PSA test to find high-grade cancers" the wording should have been "increase the ability of biopsy tissue sampling to find high-grade cancer." With finasteride or dutasteride shrinking the size of the prostate gland, random biopsy tissue sampling is more likely to come upon higher grade prostate cancer development than random sampling from an enlarged prostate gland. Interesting that now, in December 2012, the AUA and ASCO are "archiving" their 2009 stance that appears to be more a "C.Y.A" (cover your….) because, as noted in a report on The "New" Prostate Cancer InfoLink: "The "archiving" of the joint ASCO/AUA guidance document is probably (as much as anything else) a way for the two organizations to protect themselves legally from possible future accusations that they continue to "recommend" the use of 5-ARIs for chemoprevention of prostate cancer. We do, after all, live in a highly litigious society. "

Finasteride/Proscar inhibits Type II 5AR enzymes from converting testosterone to the more powerful stimulant to prostate cancer cell growth, dihydrotestosterone (DHT).

Dutasteride/Avodart inhibits both Type I and Type II enzymes from converting testosterone to the more powerful stimulant to prostate cancer cell growth, dihydrotestosterone (DHT).

In Androgen Deprivation therapy, since a higher incidence of Type I is present in high-grade prostate cancer, the prescribing of dutasteride/Avodart is recommended to accompany an LHRH agonist and/or an antiandrogen since it inhibits both Type I and Type II enzymes from converting testosterone to the much more powerful stimulant to PC cell growth, dihydrotestosterone. The LHRH agonist inhibits testicular production of testosterone; it has no effect on adrenal gland manufacture of testosterone metabolized from androgen precursors. The antiandrogen is

expected to block testosterone from binding to androgen receptors to prohibit any testosterone access to the cancer cell nucleus and consequent contact with 5AR where it is converted to the more powerful DHT. It is likely that with the multitude of androgen receptors on each cancer cell that among them will be faulty receptors, and should that be the case, testosterone from adrenal gland production can access the 5AR enzymes and be converted to DHT; thus the importance in ADT to inhibit that from occurring.

MORE:

In that the 5Alpha Reductase (5AR) inhibitors finasteride/Proscar or dutasteride/Avodart inhibit the conversion of testosterone to dihydrotestosterone, and it is well known that dihydrotestosterone is a much more powerful stimulant to prostate cancer cell growth than is testosterone, these 5AR inhibitors DO suppress existing cancer growth.

Reduction by Dutasteride of Prostate Cancer Events (REDUCE) Trial results:

http://tinyurl.com/2f7cgz2

"The mechanism of dutasteride is not primarily prevention **but the inhibition of growth of small, well differentiated cancers as a result of the intracellular reduction of 5a-dihydrotestosterone (DHT).** This mechanism which results in the prevention of disease progression is called 'tertiary prevention' and in this setting can be seen as treatment of minimal disease.

http://clincancerres.aacrjournals.org/cgi/content/abstract/10/21/7121

"*Conclusions:* The source of dihydrotestosterone in prostatic tissue after androgen deprivation therapy involves intracrine production within the prostate, converting adrenal androgens to dihydrotestosterone. Dihydrotestosterone still remaining in prostate tissue after androgen deprivation therapy may require new therapies such as treatment with a combination of 5α-reductase inhibitors and antiandrogens, as well as castration."

From renowned Medical Oncologist Charles E. "Snuffy" Myers, who also specializes specifically in the treatment of prostate cancer:

http://www.prostateforum.com/article-03-26-07.html

"Since I opened my clinic—the American Institute for Diseases of the Prostate—in 2002, I've made it a practice to measure dihydrotestosterone levels in each patient we see. And I have to tell you that medical castration, while effective at reducing testosterone from the normal range of 300-800 ng/dL to below 30 ng/dL, often leaves dihydrotestosterone levels within the normal range (30-80 ng/dL). And dihydrotestosterone is ten times more powerful than testosterone at stimulating prostate growth, so a dihydrotestosterone of 30 ng/dL is potentially as powerful as a testosterone of 300. Dihydrotestosterone formation can be blocked in most patients with either Proscar or Avodart, with Avodart being more consistently effective. I've found this can aid in inducing remission in patients who've failed Lupron. Luckily, Proscar and Avodart don't cause any additional side effects in men on hormonal therapy. But again, we have to measure dihydrotestosterone levels to see if Proscar or Avodart are in fact suppressing dihydrotestosterone. "

And more from Medical Oncologist Myers:

Question posed to Dr. Myers:

The recently published results of a large clinical trial (REDUCE), aimed at evaluating Avodart's effectiveness in reducing the incidence of prostate cancer, found a 23% risk reduction over a four-year period, a result consistent with those from earlier studies (NEJM 4/1/2010). The new study also found, however, that those taking Avodart had a higher incidence of cardiac failure than those in the placebo group (0.7% vs 0.3%), a result that I believe is a new finding. Do you consider the negative cardiac results significant and do they alter your views about Avodart's use as a preventive medication or as a treatment for prostate cancer?

Dr. Myers reply:

"I think this is a very important study on many levels. Proscar and Avodart both work by blocking the conversion of testosterone to dihydrotestosterone. As water backs up behind a dam, serum testosterone levels will typically increase as the serum dihydrotestosterone levels fall. In prostate cancer cells,

dihydrotestosterone is much more powerful at stimulating growth than testosterone. Additionally, dihydrotestosterone specifically stimulates blood flow to both normal prostate tissues and prostate cancer, while testosterone is not very effective at this. We have long had population studies that have shown the risk of prostate cancer is related to the serum dihydrotestosterone and not to the serum testosterone. This led to the hypothesis that dihydrotestosterone was a major factor fueling the appearance and then progression of prostate cancer. An earlier large randomized controlled trial showed that Proscar reduced the risk of prostate cancer, confirming the role of dihydrotestosterone in the development of prostate cancer. Now, Avodart has also been shown to significantly reduce the risk of prostate cancer. Taken together, these two large randomized controlled trials prove beyond all reasonable doubt that dihydrotestosterone is one of the causes of prostate cancer. Further, because both drugs increase serum testosterone by 20-50%, these studies show that testosterone itself is not a major factor in the progression of prostate cancer. I cannot stress how fundamentally important this is. I do not think most physicians caring for men with prostate cancer have fully thought through the implications of these findings. One implication is that as long as the testosterone receptor is present and linked to cancer growth, the presence of dihydrotestosterone has the potential to continue to fuel the progression of the cancer. The obvious question now is whether it might not be better to always suppress dihydrotestosterone.

As indicated in your question, the REDUCE trial did find an increased risk of heart failure in men in the Avodart arm compared with placebo. There were 6,729 patients randomized between

the two arms. In the placebo arm, 0.4% developed congestive heart failure compared with 0.7% in the Avodart arm. This calculates out to 13 cases in the placebo group and 23 cases in the Avodart arm. So, the additional risk of heart failure in the Avodart arm is still quite low.
Dr. Andriole, the author of the paper, has speculated that this was linked to coadministration of drugs like Flomax. Flomax and related drugs, like Hytrin and Cardura, work by blocking epinephrine at what are called alpha 1-adrenergic receptors. This class of drugs has already been reported to exacerbate heart failure and so Dr. Andriole's suggestion is very reasonable. From his comments, I gather they do not specifically know if the patients who developed heart failure on Avodart were also taking an alpha 1 blocker. So, at present, this remains a speculation.
How should we respond to this? Well, first I think that until this is clarified, Avodart should be given to men in congestive heart failure only if the patient is carefully monitored and only if the clinical benefit warrants the use of Avodart. The combined administration of Flomax and related drugs with Avodart should similarly be done with caution in general and not at all in patients in heart failure."

AND MORE….

Another case for including a 5AR inhibitor (dutasteride/Avodart or finasteride/Proscar) in ADT

http://clincancerres.aacrjournals.org/content/10/21/7121.full

Skipping to the last paragraph of the above lengthy paper for brevity:

“These findings and our results suggest that new therapies that target androgen receptor and prevent formation of androgens within prostate cancer cells such as treatment with a combination of antiandrogens and 5α-reductase inhibitors can block the stimulation from adrenal androgens that contributes ~25% of total dihydrotestosterone when they are combined with testicular suppression of androgens and may offer the most effective androgen deprivation therapy to prolong remission of prostate cancer as of now.”

Efficacy of 5α-reductase inhibitors for patients with large benign prostatic hyperplasia (>80 mL) after transurethral resection of the prostate.

http://tinyurl.com/nen8pos

As specifically noted: **“**Three years after TURP, there were significant differences in prostate volume (PV), level of prostate-specific antigen (PSA), the maximum flow rate (Qm), and HU between the trial and control groups. Additionally, there were significant differences in the PV, PSA, international prostate symptom score (IPSS), patient quality of life (QoL) in the trial group alone between those treated with finasteride and those treated with dutasteride.

CONCLUSIONS - After TURP for large BPH, administration of 5αRIs for 3 years improved PV, PSA, Qm and HU. Additionally, dutasteride produced superior improvements in PV, PSA, IPSS and QoL compared with finasteride.**“**

More at: AVODART* http://tinyurl.com/3gfd23r