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By Kevin D. Blanchet

REDUCE Trial Inspires Debate

Is dutasteride ready for widespread use as prevention for prostate cancer?

"As Andy Warhol said, everyone has their 15 minutes of fame". That's how Gerald L. Andriole, Jr, MD, described the attention he was getting at the recent American Urological Association (AUA) Annual Scientific Meeting in Chicago, Illinois. "After this is over, I'll return to being just another garden-variety urologist in St. Louis", he says. As Professor and Chief of Urology at Washington University in St. Louis, Missouri, Dr. Andriole is having more than 15 minutes of fame. On the heels of publishing his results on the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial, he is once again in the spotlight. This time, it is for the findings from his Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial on the effect of dutasteride on prostate cancer risk reduction. The late-breaking presentation at the meeting was being debated even before Dr. Andriole stepped up to the microphone.

> Clearly, the data show that dutasteride did not lead to more high-grade tumours, even though they would have been easier to detect in the dutasteride-treated men due to their smaller prostates. *Gerald L. Andriole, Jr, MD*

In the REDUCE trial, dutasteride significantly lowered the risk of prostate cancer compared with placebo, with no increase in high-grade tumours. "The drug reduced the risk of prostate cancer over four years by 23%", says Dr. Andriole, referring to the primary endpoint of the trial. "There were approximately 200 more cases of cancer occurring in men who took the placebo compared with men who took dutasteride". During the four years, 83% of the 8200 participants had at least one biopsy; 22.5% of these had prostate cancer. Dr. Andriole is quick to point out that, "only a tiny minority of cancers was the result of the protocol-independent biopsy". There was a 22.5% reduction in the

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• Abnormalities in aminotransferase levels are frequent during acute pyelonephritis. *European Journal of Internal Medicine.* 2009;20(3):e-53-e-56.

• Elevated CRP levels associated with rapid increases in irritative LUTS. *American Journal of Epidemiology.* 2009;April 24, online ahead of publication.

• Significant association found between two genes and bladder cancer. *Carcinogenesis.* 2009; 30(5):763-768.

number of prostate cancers in men receiving dutasteride during the first two years of the trial. Biopsies at four years showed an additional 23.5% risk reduction. This is the time when one would anticipate more men with cancer in the dutasteride population, because more of the cancers in the placebo arm had already been eliminated. The risk reduction observed in this trial was consistent in both young and old men, regardless of family history of prostate cancer. It was also consistent in men with varying degrees of symptoms.

Men in the dutasteride who did develop prostate cancer had no greater risk of aggressive tumours than those in the placebo group. In fact, the percentage of high-grade tumours (Gleason score of 7–10) was nearly identical in the placebo group (6.8%) and in the dutasteride group (6.7%). "I'm personally very reassured that there is no significant increase in high-grade tumours over the four years of the trial", says Dr. Andriole. "Clearly, the data show that dutasteride did not lead to more high-grade tumours, even though they would have been easier to detect in the dutasteride-treated men due to their smaller prostates".

However, not everyone is as convinced or reassured as Dr. Andriole. At the press conference that followed his presentation, there were as many urologists as reporters in the standing room–only crowd. One of them was William J. Catalona, MD, professor of urology at Northwestern Feinberg School of Medicine and Director of the Clinical Prostate Cancer Program at Northwestern Memorial Hospital in Chicago, Illinois. He tells "UroScan" that he and others were very concerned that dutasteride can mask high-grade cancers and create a false sense of well-being in men. "These drugs are effective at shrinking benign enlargement of the prostate and even handling some of the low-grade cancer elements, but they can't handle the Gleason grade 8, 9 and 10 tumours that really kill patients", he says.

Dr. Catalona remembers the difficulties surrounding the Prostate Cancer Prevention Trial (PCPT), which was halted early in 2003 after finasteride was found to reduce the incidence of prostate cancer. However, men who did develop prostate cancer while on the drug had a slightly higher incidence of high-grade tumours. Later, a post-hoc analysis using computer modelling found fewer high-grade cancers with finasteride, a finding Dr. Catalona calls "a stretch". He sees the same issues with the REDUCE trial, in which there were 29 high-grade cancers (Gleason score 8–10) in the dutasteride arm and 19 in the placebo arm. "With larger numbers of patients, I think this would have been statistically significant", says Dr. Catalona.

He also believes the study is too short to be making any sweeping conclusions, particularly because the four-year results are not surprising. "Any form of hormonal therapy is going to mask the cancer for a while, but we know that it never cures the cancer when used as treatment. Eventually, the effect wears off". Citing the PCPT again, he points out that by the seventh year, the effect of finasteride had completely worn off. By then, the study was not detecting that many fewer cancers in the finasteride group than in the placebo group. "If you design a four- or seven-year study and then quickly end it, you are more likely to get a favourable-looking result", he says.

After Dr. Andriole's presentation, a prominent urologist shared with Dr. Catalona his experience with a patient who had an enlarged prostate and a high prostate-specific antigen (PSA) level but showed no cancer upon biopsy. He prescribed generic finasteride, and as expected, the man's PSA level went down and he felt better. Before long, however, the PSA level started increasing. Believing that the generic might not be as good as the brand-name

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Clinical Trial 1

TITLE:

Temsirolimus Versus Sorafenib as Second-Line Therapy in Patients With Advanced Renal Cell Carcinoma (RCC) Who Have Failed First-Line Sunitinib

PROTOCOL ID:

NCT00474786

SUMMARY:

This is an international, randomized, open-label, outpatient multicenter study. Subjects will be assigned in a one-to-one ratio to one of two treatment arms. The first arm will be temsirolimus 25 mg once weekly by intravenous infusion; the second arm will receive sorafenib 400 mg by mouth twice daily. Both drugs will be administered in six-week cycles for the duration of the study, up to 24 months. Subjects will be stratified by nephrectomy status, duration of response to sunitinib therapy, Memorial Sloan Kettering Cancer Center prognostic group and RCC tumor histology.

ELIGIBILITY:

Subjects must have a histologically-confirmed diagnosis of metastatic RCC with well-documented radiological progressive disease by Response Evaluation Criteria in Solid Tumors (RECIST) or clinical progressive disease as judged by the investigator while receiving first-line sunitinib therapy. In addition, subjects must have at least one cycle of sunitinib therapy (minimum of four weeks continuously). At the time of randomization and at least two weeks since prior treatment with sunitinib, patients should have undergone palliative radiation therapy and/or surgery. All toxic effects of prior therapy need to be resolved. At the time of randomization, there must be at least one measurable lesion per RECIST. Lesions that have been previously irradiated or embolized cannot be selected as target lesions.

LOCATIONS AND CONTACT:

114 study locations worldwide. Contact the trial manager at clintrialparticipation@wyeth.com.

drug, the urologist switched his patient to Proscar. The patient's PSA level decreased slightly but then immediately started to increase again. "Finally, he put the patient on dutasteride, which blocks both of the enzymes", recounts Dr. Catalona of the anecdote he heard. "Again, the PSA [level] went down a bit then started going back up. At this point, he biopsies the man and finds Gleason 8 cancer in virtually every core. I have experienced this myself a number of times".

Dr. Catalona is also concerned that prescribing dutasteride to prevent prostate cancer will interfere with the valuable use of PSA velocity measurements. Using PSA velocity to detect prostate cancer is very controversial. In addition to the PCPT, the European Randomized Study of Screening for Prostate Cancer [1] claims that PSA velocity is not useful for detecting life-threatening prostate cancer. Dr. Catalona sees these studies as having serious flaws due to the lengthy time frames when PSA velocities were taken. "You measure PSA velocity from the present to a time in the past. To the extent that the PSA represents the amount of cancer, the PSA velocity today is faster than it was yesterday. If you measure the PSA velocity from today to a year ago, you would have a steeper slope than if you measured it from today to two years ago or four years ago when the slope gets progressively flatter". He sees measuring PSA velocity between such long time points as being dangerous. "I feel you have to measure it over the past year to have the PSA velocity be relevant to what the tumour is actually doing today". One study from Johns Hopkins in Baltimore, Maryland has used PSA velocity measurements correctly to show that the method can detect cancers with bad pathologies that are likely to recur and cause death [2].

Measuring PSA velocity starting at an early age and again every year thereafter will identify some men who have lethal cancers, believes Dr. Catalona. "A lot of these men are not able to be identified and salvaged with the way we are doing things today", he says. For him, PSA velocity is a way of potentially saving a group of men who will die of prostate cancer because they are not being identified. By using dutasteride, "you may be removing a really valid method of detecting cancer earlier, particularly in young, high-risk men". A good example is a current patient of Dr. Catalona's, a man whose twin brother died of prostate cancer in his early 50s. "If you put someone like him on dutasteride, he'll think it is going to prevent him from getting prostate cancer. The PSA [level] will go down as the [benign prostatic hyperplasia] (BPH) regresses, then the PSA velocity will be the low type you get from these high-grade cancers that don't produce as much PSA per cell. It will take the PSA velocity a longer time to rise to a suspicious level. However, if he had the PSA contribution from the BPH and from his low- and high-grade elements, the cancer would be identified earlier".

Perhaps the REDUCE and PCPT studies illustrate the pressures faced by those who have a vested interest in positive results in prostate cancer research—particularly when millions of dollars are spent on trials such as PCPT. "Back then, the feeling among a lot of urologists was that finasteride was a form of hormonal therapy", recalls Dr. Catalona. "The drug will slow down the emergence of prostate cancer by masking it, but not truly prevent it". He believes that some within the urology community believe that everyone should discuss with patients the option of using these drugs to prevent prostate cancer—although they choose their words very carefully. "They try to avoid saying 'prevents prostate cancer.' Instead, they use the phrase 'prevents prostate cancer detection', which is a little different. However, my sense is that a great majority of urologists feel this is basically trying to encourage them to use these drugs off-label, since neither dutasteride or finasteride are approved for prostate cancer prevention".

REFERENCES

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2. Carter HB, Ferrucci L, Kettermann A, et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *J Natl Cancer Inst* 2006; 98: 1521–7.

DRUG AND TECHNOLOGY NEWS

AUA COUNTERS MAINSTREAM RECOMMENDATIONS ON PSA TESTING

Contrasting recent recommendations issued by other groups, the American Urological Association (AUA) has issued new clinical guidance on prostate cancer screening, which asserts that prostate-specific antigen (PSA) level testing should be offered to well-informed men aged 40 years or older who have a life expectancy of at least 10 years. According to the Best Practice Statement, the PSA test, when offered and interpreted appropriately, may provide essential information for the diagnosis, pre-treatment staging, risk assessment,

> Prostate cancer testing is an individual decision that patients of any age should make in conjunction with their physicians and urologists. *Peter Carroll, MD*

and post-treatment monitoring of prostate cancer.

"The single most important message of this statement is that prostate cancer testing is an individual decision that patients of any age should make in conjunction with their physicians and urologists", says Peter Carroll, MD, who chaired the panel that developed it. "There is no single standard that applies to all men, nor should there be at this time". Before finalizing the new guidelines, the panel reviewed the most recently reported trials of PSA level testing in both the United States and Europe.

According to the statement, men who wish to be screened for prostate cancer should have both a PSA level test and a digital rectal examination (DRE). In addition, other factors such as family history, age, overall health and ethnicity should be combined

with the results of PSA level testing and physical examination in order to better determine the risk of prostate cancer. The benefits and risks of screening of prostate cancer should be discussed, including the risk of over-detection.

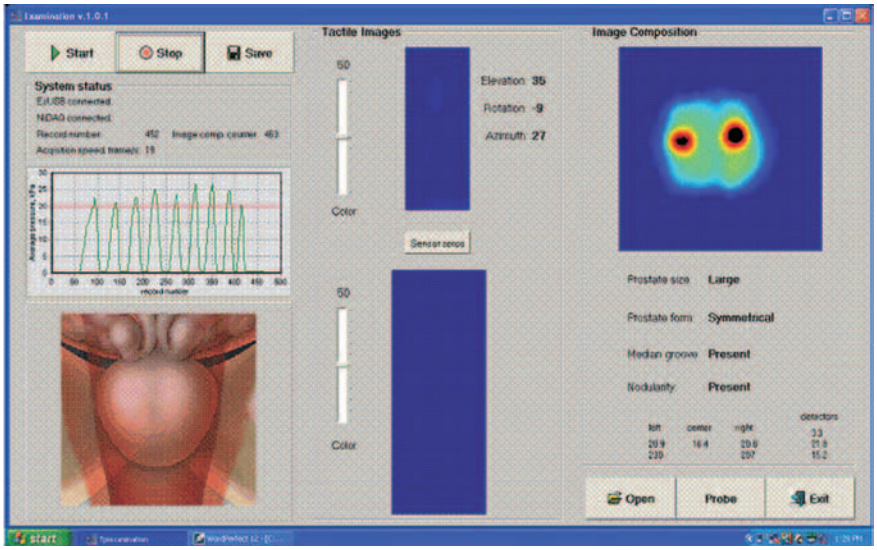
In regard to biopsy, a continuum of risk exists at all values. Major studies have demonstrated that there is no safe PSA value below which a man may be reassured that he does not have biopsy-detectable prostate cancer. Therefore, the AUA does not recommend a single PSA level threshold at which a biopsy should be obtained. Rather, the decision to perform a biopsy should take into account additional factors, including free and total PSA levels, PSA velocity and density, patient age, family history, race/ethnicity, previous biopsy history and co-morbidities. The statement emphasizes that not all prostate cancers require active treatment and that not all prostate cancers are life threatening. The decision to remain in surveillance or to proceed to treatment is one that men should discuss in detail with their urologists. "Prostate cancer comes in many forms, some aggressive and some not", Dr. Carroll points out. "But the bottom line about prostate cancer testing is that we cannot counsel patients about next steps for cancers that we do not know exist".

Additionally, the Best Practice Statement clarifies a number of key points about the use of PSA levels in treatment selection and post-treatment follow up of prostate cancer patients. It is available online at www.AUAnet.org. There is also an official Patient Guide outlining what men need to know when it comes to prostate cancer testing.

Prostate Imaging Device Makes Debut

At the American Urological Association (AUA) Annual Scientific Meeting in Chicago, Illinois, an adjunctive tool to digital rectal examination (DRE) was showcased to attendees. Called the ProUroScan System, the new device is an imaging system designed to provide a map of the prostate and to store a digital image of that map for review. It is intended to be used after a physician identifies abnormal tissue during a DRE. The first generation system will provide a map or record of the pressures that are generated from palpation of the posterior surface of the prostate using a sensor probe. Its operation is based on measurement of the stress pattern on the rectal wall when the probe is pressed against the prostate. Temporal and spatial changes in the stress pattern provide information on the elastic structure of the gland and allow two-dimensional reconstruction of prostate anatomy and visualization of prostate mechanical properties. The data acquired then allow the calculation of prostate features, such as size and shape. The prostate image is displayed on a screen that allows physicians to visualize tissue abnormalities in the prostate gland. In addition to the real time visual image, the results are stored electronically.

To perform a scan, the clinician inserts the tip of the probe into the patient's rectum and palpates the prostate. As the prostate is palpated, a colour image of the prostate is produced and displayed on the computer monitor, along with indicators of the amount of pressure being applied, to help guide the clinician. Differences in tissue stiffness and elasticity are depicted in real time on a colour monitor. Total testing time for a healthy prostate is under one minute.



The ProUroScan System provides a digital map of the prostate.

The first generation ProUroScan System has been tested in laboratory experiments on prostate models and in a pre-clinical study. In addition, the system was used for over two years on approximately 168 patients at the Robert Wood Johnson Medical Center in New Brunswick, New Jersey. A 40-patient clinical trial conducted by four different physicians is currently underway. System optimization is still required in the areas of positioning system refinement, software, validation, probe sterilization, user interface and sensor production. The system is currently for investigational use only, although plans are underway for FDA approval.