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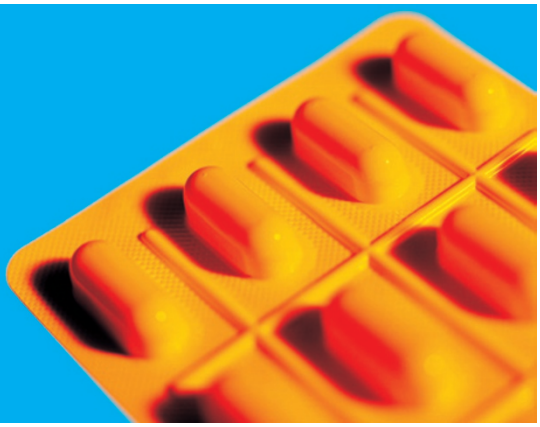
PROSTATE CANCER

Third time lucky? Dutasteride for tertiary prevention of prostate cancer

Evidence of the efficacy of dutasteride for prostate cancer prevention is piling up. New research, published in *European Urology*, suggests that dutasteride treatment can provide protection against disease progression for patients who have undergone radical prostatectomy or radiation therapy for prostate cancer.

Dutasteride (marketed as Avodart® by GlaxoSmithKline [USA]) is a dual 5α-reductase inhibitor (5ARI) that hit the headlines in 2011 when the FDA made the decision not to approve its use for the primary prevention of prostate cancer despite promising results from the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. After REDUCE came REDEEM (Reduction by Dutasteride of Clinical Progression Events in Expectant Management), which demonstrated a role for dutasteride in the secondary prevention of prostate cancer, owing to its ability to slow disease progression in patients with low-risk prostate cancer under active surveillance.

Now, a research team led by Fritz Shröder has reported the results of the Avodart® after Radical Therapy for Prostate Cancer Study (ARTS), a randomized placebo-controlled double-blind clinical trial designed to evaluate the efficacy of dutasteride for the tertiary prevention of prostate cancer—in other words, its ability to delay disease progression in patients for whom curative therapy has failed. "Our efforts were fuelled by the recent FDA decision not to allow the use of 5ARIs for prevention of prostate cancer," explains Schröder. "Our data cast doubt on some of the key arguments used by the FDA."



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Most patients with early-stage prostate cancer undergo either radical prostatectomy or radiotherapy as primary treatment, but it has been estimated that 27–53% of these men experience recurrence within 10 years. Based on the findings of a previous study, reported by Gerald Andriole and colleagues, which demonstrated that the 5ARI finasteride could delay PSA progression, Schröder and his team started ARTS to evaluate whether dutasteride could delay or prevent the progression of prostate cancer in patients with biochemical failure after definitive treatment.

ARTS accrued 294 men with asymptomatic PSA failure, which was defined according to the EAU guidelines for patients who had undergone radical prostatectomy and the Radiation Therapy Oncology Group–American Society for Therapeutic Radiology and Oncology 2005 Consensus Conference for those who had received radiation therapy. These men, from 64 centres across nine countries in Europe, were randomized to receive either 0.5 mg dutasteride ($n = 147$) or placebo ($n = 147$) once daily for 2 years, with PSA doubling time as the primary end point. After 2 years of treatment, dutasteride was found to significantly delay PSA doubling time compared with placebo, with a relative risk reduction of 66.1% (95% CI 50.35–76.90; $P < 0.001$).

Investigators chose to assess PSA doubling time because increasing PSA level is often the first indication of recurrence in these men, and is known to predate the clinical detection of metastatic disease by several years. To reinforce their findings, they analysed time to disease progression as a secondary end point, with a broad definition of disease progression that included PSA doubling time of ≤3 months, biopsy-confirmed increase in clinical T stage, the need for salvage therapy, and the presence of bone metastases. Using these criteria, dutasteride significantly delayed disease progression compared with placebo, with a relative risk reduction of 59% (95% CI 32.53–75.09; $P < 0.001$). "If the speed of PSA rise is decreased, and if this correlates with parameters of clinical progression, this in my view proves an effect of the drug on prostate cancer growth," says Schröder. "These findings are in line with the recently published REDEEM study, but not with the argumentation of the FDA."

The use of salvage therapy and the development of bone metastases are indeed indicators of clinical progression, but the number of patients affected in this study was small, and the effect of dutasteride on these parameters requires confirmation. Schröder told *Nature Reviews Urology* that a larger study with longer duration of follow-up and clinical progression as a primary end point would be the next step.

"In the meantime, it is left to the medical community to decide how to apply our results," Schröder concludes. "I routinely offer a 5ARI to men with rising PSA levels as an alternative to radiotherapy or watchful waiting." There is no denying that a medical treatment capable of delaying cancer progression with minimal adverse effects must be an appealing option for men experiencing biochemical failure.

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Original article Schröder, F. *et al.* Dutasteride treatment over 2 years delays prostate-specific antigen progression in patients with biochemical failure after radical therapy for prostate cancer: results from the randomised, placelbo-controlled Avodart after radical therapy for prostate cancer study (ARTS). *Eur. Urol.* doi:10.1016/j.eururo.2012.11.006