MAYO CLINIC

ORIGINAL ARTICLE

5-Alpha Reductase Inhibitors and the Risk of Prostate Cancer Mortality in Men Treated for Benign Prostatic Hyperplasia

Lauren P. Wallner, PhD, MPH; Julia R. DiBello, PhD; Bonnie H. Li, PhD; Stephen K. Van Den Eeden, PhD; Sheila Weinmann, PhD; Debra P. Ritzwoller, PhD; Jill E. Abell, PhD; Ralph D'Agostino Jr, PhD; Ronald K. Loo, MD; David S. Aaronson, MD; Kathryn Richert-Boe, MD; Ralph I. Horwitz, MD; and Steven J. Jacobsen, MD

Abstract

Objective: To compare the risk of prostate cancer mortality among men treated with 5- alpha reductase inhibitors (5-ARIs) with those treated with alpha-adrenergic blockers (ABs) in community practice settings.

Patients and Methods: A retrospective matched cohort (N=174,895) and nested case-control study (N=18,311) were conducted in 4 regions of an integrated health care system. Men 50 years and older who initiated pharmaceutical treatment for benign prostatic hyperplasia between January 1, 1992, and December 31, 2007, and had at least 3 consecutive prescriptions were followed through December 31, 2010. Adjusted subdistribution hazard ratios, accounting for competing risks of death, and matched odds ratios were used to estimate prostate cancer mortality associated with 5-ARI use (with or without concomitant ABs) as compared with AB use.

Results: In the cohort study, 1,053 men died of prostate cancer (mean follow-up, 3 years), 15% among 5-ARI users (N= 25,388) and 85% among AB users (N=149,507) (unadjusted mortality rate ratio, 0.80). After accounting for competing risks, it was found that 5-ARI use was not associated with prostate cancer mortality when compared with AB use (adjusted subdistribution hazard ratio, 0.85; 95% CI, 0.72-1.01). Similar results were observed in the case-control study (adjusted matched odds ratio, 0.95; 95% CI, 0.78-1.17).

Conclusion: Among men being pharmaceutically treated for benign prostatic hyperplasia, 5-ARI use was not associated with an increased risk of prostate cancer–specific mortality when compared with AB use. The increased prevalence of high-grade lesions at the time of diagnosis noted in our study and the chemoprevention trials may not result in increased prostate cancer mortality.

 ■ Mayo Clin Proc. 2016;■■(■):1-10

The use of 5-alpha reductase inhibitors (5-ARIs) along with alpha-adrenergic blockers (alpha-blockers [ABs]) to manage lower urinary tract symptoms (LUTSs) associated with benign prostatic hyperplasia (BPH). Because 5-ARIs inhibit the conversion of testosterone to dihydrotestosterone, which reduces prostate size, they have been suggested as potential chemopreventive agents for prostate cancer. To assess this, 2 randomized trials were conducted, the Prostate Cancer Prevention Trial (PCPT)[1] and Reduction by Dutasteride of Prostate Cancer Events,[2] which found a reduced risk of prostate cancer of 23% to 25% when compared with placebo. There was, however, an increase in high-grade (Gleason 7-10) cancers among the 5-ARI group in the PCPT and a significant increase in years 3 and 4 of the Reduction by Dutasteride of Prostate Cancer Events trial.[1,2] Because it was not possible to determine whether the association was a result of bias or an effect of the drugs, uncertainty continues to exist regarding the use of 5-ARIs for the chemoprevention of prostate cancer.[3-5]

From the Department of Medicine, University of Michigan, Ann Arbor, MI (L.P.W.); Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA (L.P.W., B.H.L., R.K.L., S.J.J.); Worldwide Epidemiology, GlaxoSmithKline, Collegeville, PA (J.R.D.); Division of Research,

Affiliations continued at the end of this article.

Before the safety of using 5-ARIs for the primary prevention of prostate cancer can be established, studies assessing their long-term use in community practice settings are necessary.[6,7] However, the studies to date were limited by the use of total mortality rather than prostate cancer–specific mortality and the rarity of this outcome, limited information on dose and duration, and importantly, the use of highly-selected populations that have limited generalizability to clinical practice.[8-10] Therefore, the goal of this study was to specifically assess the risk of prostate cancer–specific mortality associated with 5-ARIs use as compared with AB use for the treatment of BPH/LUTSs in a large population-based cohort of 214,272 men in community practice settings over a 19-year observation period.

METHODS

Study Population

This study was conducted in 4 regions of Kaiser Permanente (Northern and Southern California, Colorado, and Northwest) that are each integrated health care systems that collectively provide comprehensive health care services to more than 8.5 million members. The racial and socioeconomic diversity of the members closely reflects that of the regions each serves.[11] Comprehensive electronic health records along with the standardized Virtual Data Warehouse[12] allow for the collection of demographic characteristics, health services utilization, disease diagnoses, and death records and includes pharmacy data and inpatient, outpatient, and emergency department encounters, as well as care received outside of the system. This study was approved by the institutional review boards at each site.

A cohort of male members aged 50 years and older who received a new prescription for a BPH/LUTS medication between January 1, 1992, and December 31, 2007, and were members for at least 1 year before first dispensing were eligible for inclusion (N=281,034). Men with a diagnosis of prostate cancer before or within 3 months of their first prescription (n=20,170), those with less than 90 days of consecutive medication filled (n=44,516), and those treated with finasteride 1 mg for alopecia (n=2023) and men with incomplete data (N=82) were excluded, leaving 214,272 men eligible for matching (Figure).

Exposure Assessment

The primary exposure of interest was a new prescription for a 5-ARI or an AB from 1992 to 2007 identified via prescription fills in electronic pharmacy records. Because of variability in the availability of pharmacy records in each region, the start dates were 1992 (Southern California, Northwest, and Colorado) and 1995 (Northern California). Men with exposure to either medication class before baseline were excluded. Combination users (men who were exposed to both an AB and 5-ARI) were defined as 5-ARI users for matching purposes in both studies. In the cohort study, combination users contributed person-time to both exposure groups. However, in the case-control study, men were defined as 5-ARI users if they ever used a 5-ARI. Cumulative exposure and dose were calculated from 5-ARI initiation in men who were 5-ARI users and corresponding matched index date among AB users in the cohort study and from 5-ARI initiation among 5-ARI users and AB initiation among AB users in the nested case-control study.

Outcome Assessment

The primary outcome was prostate cancer–specific mortality, which was identified via a comprehensive search across multiple sources for vital status. This included local (regional) Kaiser Permanente death databases, cancer registries, state death records, a Social Security Death Index Match, and National Death Index Match. Prostate cancer death was then defined on the basis of coded underlying or primary cause of death.

Matching

Cohort Study. Men who initiated a 5-ARI were matched using risk-set sampling 1:6 to alpha-blocker users on age at matching (±2 years), race (African American vs Other), timing of BPH medication initiation (within 2 years), history of AB use, and health plan region. Of the 214,272 eligible men, 73% were successfully matched, resulting in an analytic sample of 157,456 men with 174,895 records (18,321 men were matched as both a

Mayo Clin Proc. ■ XXX 2016;■■(■):1-10 ■ http://dx.doi.org/10.1016/j.mayocp.2016.07.023
www.mayoclinicproceedings.org