Review

CellPress

Statins: protectors or pretenders in prostate cancer?

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The role of statin therapy in prostate cancer (PCa) prevention and treatment is plagued by controversy. This critical review of published clinical series reveals several caveats in earlier studies, which reported no benefit. Recent studies that adjust for confounding factors have demonstrated statin therapy to be associated with PCa prevention and favorable clinical outcomes. Developed as inhibitors of cholesterol synthesis, the expected mechanism of statin action is systemic cholesterol reduction. By lowering circulating cholesterol, statins indirectly reduce cellular cholesterol levels in multiple cell types, impacting on membrane microdomains and steroidogenesis. Although non-cholesterol mechanisms of statin action have been proposed, they are limited by the uncertainties surrounding *in vivo* tissue statin concentrations.

Are statins a useful therapy in the fight against PCa?

PCa is the most commonly diagnosed cancer in men [1]. Although androgen-deprivation therapy may slow and temporarily reverse tumor progression, the clinical response to this therapy inevitably changes, a state termed castration-resistant PCa, for which there is currently no cure [2]. Over the past 15 years a beneficial link between the use of the 'statin' class of FDA-approved cholesterol-lowering drugs and PCa has been suggested. In this article we critically review the current evidence from clinical studies and the range of possible molecular mechanisms of statins in PCa prevention and therapy.

Clinical studies of statins in PCa

Important considerations

Following FDA approval for treating hyperlipidemia in 1987, statins have become among the most commonly prescribed medications worldwide, and are ingested regularly by 25% of adults aged 45 years and over in the USA [3]. Importantly, use of these drugs provides significant benefits in primary and secondary prevention of major occlusive vascular events [4]. These medications have well-studied side-effect profiles and are generally tolerated without concerns (discussed in Box 1), to such an extent

Glossary

Abiraterone acetate: an inhibitor of cytochrome P450 17α-hydroxylase/17,20-lyase (CYP17), a key enzyme that catalyzes the biosynthesis of androgens from pregnane precursors. FDA-approved for metastatic castration-resistant PCa patients.
Adrenal gland: an endocrine organ and extra-testicular source of androgens. Production of these androgens may be considered a therapeutic target in castration-resistant PCa patients.
Biochemical recurrence (BCR): also called biochemical failure, is defined as an increase in serum PSA following treatment for PCa with curative intent.
Ezetimibe: a drug that inhibits intestinal cholesterol absorption by binding to Niemann–Pick C1-like 1 (NPC1L1) protein. Often considered for combination therapy with statin in hyperlipidemic patients.
Fibrates: agonists of peroxisome proliferator-activated receptor-α (PPAR-α); lipid-lowering medications that reduce triglyceride-rich lipoproteins by inhibiting the synthesis of very low density lipoprotein (VLDL).
Liver X receptor (LXR): a sterol-activated nuclear transcription factor which participates in cellular cholesterol efflux.
Myositis: muscular pain or discomfort from infection or other causes such as autoimmune diseases.
Niacin: a type of vitamin B (vitamin B_3 or nicotinic acid). Can be used as a lipid-lowering drug.
Prostate cancer (PCa): an adenocarcinoma arising from the prostatic epithelium.
Prostate-specific antigen (PSA): a serine protease of the kallikrein-related peptidase family that is released by prostate epithelial cells. Often observed to be elevated in the serum of PCa patients, hence its use as a biomarker.
Resins: bile acid resins used as lipid-lowering agents; they bind to cholesterol-derived bile acids, reducing their absorption and thus their enterohepatic recirculation from the small intestine.
Rhabdomyolysis: the destruction or degeneration of skeletal tissues with massive release of proteins (creatine kinase) into the bloodstream, potentially causing end-organ failure.
Sterol-regulatory element-binding protein (SREBP): a transcription factor that enables cholesterol synthesis and uptake. Three isoforms are found in mammals: SREBP-1a, SREBP-1c, and SREBP-2. SREBP-1 participates in fatty acid synthesis whereas SREBP-2 is involved in cholesterol metabolism.
Statin: a class of drugs that competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme in the mevalonate pathway which is involved in cholesterol synthesis and the formation of isoprenoid lipid anchors (prenylation). Statins inhibit the mevalonate pathway but also increase the expression of low-density lipoprotein (LDL) receptors in hepatocytes, thereby reducing circulating blood cholesterol levels. Hydrophobic (lipophilic) to hydrophilic (lipophobic) statins (in order of hydrophobicity): lovastatin > simvastatin > atorvastatin >> fluvastatin > rosuvastatin > pravastatin.

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Keywords: statin; HMG-CoA reductase; prostate cancer; cholesterol; androgen synthesis; prenylation.

1043-2760/$ – see front matter
 http://dx.doi.org/10.1016/j.tem.2013.12.007

Box 1. Side-effects of statins

The most common side-effects of statins include muscle-related symptoms (myalgia in 0.1–15% of patients) and liver enzyme elevations, which may result in patients not taking their medication [65–67]. True incidence estimates of adverse events of statins may be higher, as described in observational studies and post-marketing surveillance data, owing to reporting and patient selection in initial studies as well as a lack of consensus definitions [66,67]. However, severe muscle conditions such as myopathy (0.0002%), myositis (0.03%), and rhabdomyolysis (0.002%) are rare in people taking commercially available statins [65]. Further meta-analyses have also shown these risks are not significantly increased when compared with placebo [68]. Other rare potential side-effects include gastrointestinal and urinary tract dysfunctions, autoimmune disorders, and cardiac dysfunctions such as atrial fibrillation and bradycardia [65]. When combined with other drugs (i.e., warfarin) that are metabolized by similar liver enzymes, adverse reactions may be more frequent because of enzyme competition and the resulting higher concentrations of circulating statin [65]. The etiology appears to be multifactorial, being statin-specific (type, dose, metabolism, drug interactions) and relating to patient factors (age, other medical conditions, genetics) [66–68]. However, various algorithms may predict risk of statin-associated adverse effects [66], and strategies exist for the management of adverse effects [68].

that they have been suggested as an important part of a smart drug combination advocated for the populace at large [5].

However, contradictory findings have been reported for statins in PCa. Older studies are mostly observations of large populations or evaluations of databases from other trials in case–control or cohort formats, which were often underpowered and failed to adjust for confounding factors such as serum prostate-specific antigen (PSA; see Glossary) [6]. Clinical use of serum PSA as a surrogate marker for PCa is common, resulting in a higher incidence of PCa diagnosis and treatment [7]. To compound complexities, serum PSA is also reduced with obesity, a condition that contributes to higher rates of advanced and aggressive PCa [8,9]. Furthermore, even statins are known to reduce serum PSA [10–16], and this may complicate the utility of serum PSA in this population further because it may reduce the index of suspicion for PCa and the need for prostate biopsy-based diagnosis. Overall, it is clear that reports on statins and PCa should be assessed in an informed manner, especially with respect to numbers of PCa cases and adjustment for serum PSA and other clinical variables, together with informed assessment of data collection and reporting methods.

There are many reports of no beneficial or harmful effects of statins on PCa-specific endpoints. Of note, Chan and colleagues studied data collected as part of a prospective study on male osteoporotic fractures and found no association between statin use and PCa endpoints (total, low/high stage, low/high grade PCa), with adjustment for standard clinical parameters but not PSA, presumably because they did not possess these data [17]. Similarly, Vinogradova *et al.* used a series of nested community-based case–control series of statin users with primary cancers (n = 88 125) and matched controls (n = 362 254), but did not find any beneficial association with PCa [18].

When adjustments for serum PSA are made, an association between statin use and reduced risk of diagnosis of PCa (overall), aggressive, and fatal disease has been reported [10,12,15,19,20]. Geybels and colleagues reported that, in a retrospective evaluation of 1001 patients who were interviewed prior to PCa diagnosis, and clinical outcome determined using the Surveillance, Epidemiology, and End Results program (SEER) registry, PCa specific mortality was lower (1 vs 5% at 10 years), with cancer stage determined to be favorable in statin users [10]. Breau and colleagues examined a longitudinally based cohort with biennial examinations and observed that statin users demonstrated a reduced risk of undergoing prostate biopsy or high-grade PCa diagnosis [19]. In addition, a longer duration of statin use was associated with a lower risk for adverse PCa outcomes and a reduced likelihood of returning an abnormal PSA result when compared to a given age-specific PSA reference range. This relationship of duration of statin use with PCa outcomes may be dose-dependent, with Lustman and colleagues observing this relationship in 1813 PCa cases in a population of 66 741 patients, supporting a longer duration of statin use being associated with decreased PCa incidence, whereas a stronger association was observed for increasing total dose, for both hydrophilic and hydrophobic statins [20].

These observations were further confirmed when associations between statin use and PCa were examined by Murtola and colleagues in the Finnish PCa screening trial of 23 320 men with 9 years of follow-up [12]. They found that statin use was associated with reduced PCa incidence, and reported a dose-dependent (cumulative amount used) relationship for users of commonly prescribed statins, including simvastatin, atorvastatin, and fluvastatin. Statins outperformed other hypolipidemic agents [fibrates, acipimox (niacin), and resins], although this group was substantially smaller (n = 437) than the statin (n = 6692) or non-user (n = 16 516) groups. Users of statins and other hypolipidemic agents demonstrated lower serum PSA levels and higher free (unbound) to total PSA ratios, with a lower ratio often associated with PCa [21]. In addition, relative risk of PCa was reduced in patients undergoing prostate biopsy.

A recent meta-analysis of statin use and risk of PCa based on 27 observational studies (15 cohort, 12 case–control), with a pooled population of 1 893 571 men and 56 847 cases of PCa, reported a significant 7% reduction in risk of overall PCa [6]. A more striking and clinically valuable finding was the 20% reduction in advanced PCa. An association with long-term statin use was not established, but a cumulative trend of change in risk reporting from positive to negative was observed for the period 1993–2011. There was a significant inverse association between risk of total PCa and statin use in studies published after 2007, without publication bias, presumably with more consistent adjustment for PSA. The follow-up periods for most included studies were extensive (median 8.5 years) given that PCa is known to be a slowly growing disease and a life-expectancy of >10 years is required to provide evidence for a survival benefit from screening [22]. However, risk adjustment for possible geographical influence on PCa risk and statin use was not performed, and remains undetermined to our knowledge. This meta-analysis provides a timely summary, highlighting the shift in recent trends in evidence in favor