Statins and Malignancies in Cardiovascular Practice

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Abstract: Statins have a proven efficacy in lowering of plasma cholesterol and reduction of atherosclerotic cardiovascular disease. They also have anti-inflammatory, pro-apoptotic and anti-angiogenic effects which can be derived from their biochemical activity. The cell cycle could also be arrested at several stages. However, an early concern was the possibility of increase in malignancy. The first reports were conflicting.

A search in Web of Science has been made with the terms “statins AND malignancy”, from 2012 to 2017.

Twenty of 119 manuscripts were considered as useful. Manuscripts dealing with in-vitro and animal experiments were excluded, as well as reviews and manuscripts not related to the topic. There was a variety of malignancies under scrutiny. Most series showed a favorable result on either reduction of incidence in malignancy or, if a malignancy was diagnosed and improvement in overall or cancer specific survival. Reduction in symptoms and improvement in inflammatory response after adjuvant chemo and radiotherapy were documented in a few reports.

Elimination of bias has been attempted by taking into account confounding factors or by using a propensity analysis or a multivariate regression. Interpreting these results is difficult due to the differences in study designs. This precluded a meta-analysis. The disentangling of the effect of statins on malignancy, plasma cholesterol and changes of this level in these patients requires a large multicenter prospective trial which might encounter ethical and logistical difficulties.

Keywords: Statins, Malignancy, Survival, Atherosclerosis, Cholesterol.

INTRODUCTION

Atherosclerotic cardiovascular disease and malignancy are the two main conditions burdening health care [1]. Statins have been introduced as treatment of lipid disorders and have successfully reduced the number of cardiovascular events. However, some theoretical concerns have been issued [2]. These include non-cardiovascular events and more specifically a potential increase in cancer risk. A U-shaped relationship between cholesterol – especially HDL – and cancer [2] and a J-shaped relation with mortality have been observed. The causality is still a matter for debate, but thus far, there is no plausible reason that low cholesterol is a causative factor for cancer. With increased longevity, competing causes for mortality becomes a more complex issue. Genetic lipid disorders give an unclear answer.

Cancer in itself might attenuate atherosclerosis, based on autopsy reports. This might be clouded by the effect of age (as in prostate cancer), of cancer treatment and of cachexia. In hematological malignancies, especially with involved T-cells this might even be more present. The duration of the oncologic disease and reversibility of early atherosclerosis also might play a role. It should also be noted that there is an observed discrepancy between aortic and coronary atherosclerosis. Therefore, this cannot be considered as “one homogenous disease” [1].

Statins act as an inhibitor of hydroxy-methyl-glurataryl Coenzyme A (HMG CoA) reductase inhibitor, which is the rate-limiting step. The pleiotropic effect of statins can be explained by the biochemical pathways that are blocked. From acetate, through HMG-CoA, mevalonate, isopentylpyrophosphate, and geranyl pyrophosphate, farnesyl pyrophosphate is synthesized. The latter molecule is at a cross-road from which several pathways originate [3]. First, farnesyl pyrophosphate can be used to farnesylate proteins which play an important role is cell signaling. Second, from farnesyl, geranylgeranyl pyrophosphate can be synthesized. Geranylgeranylated proteins play a role in the Ras-family of proteins, and hence in the activation of cell surface receptors, with cell maturation, proliferation and migration. Third, geranylgeranyl pyrophosphate is a step in ubiquinone formation and cell respiration. Fourth, geranylgeranyl pyrophosphate is also a step in dolichol formation and the synthesis of glycoprotein. Fifth, farnesyl pyrophosphate is a step in the formation of squalene and hence cholesterol. This is a vital part of cell membranes and determines permeability, signal transduction and transmembrane exchange.

The pleiotropic effects of statins include inhibition of HMG-CoA reductase (lowering LDL-cholesterol), an

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increase in Apo B/E receptor and Apo B/E containing particles, promotion of apoptosis, improvement of endothelial cell function with inhibition of angiogenesis at higher dose [through inhibition of VEGF mediated signals], anti-inflammatory with immune modulating and anti-oxidant effects [3]. Because of its effects on the cell cycle, it might be postulated that statins could play a role in lower cancer rates and improved survival. Results, thus far seem inconsistent and there is a discrepancy between results of in-vitro experiments, animal experiments and clinical outcome. For the sake of simplicity, no distinction is made between lipophilic and hydrophilic statins, although the former have a lower bioavailability but the latter are less effective at. intracellular level

METHODS

A search in Web of Science has been made with the terms “statins AND malignancy”, from 2012 to 2017. There were 119 hits. Forty manuscripts were not related to the topic. Exclusion criteria were letters to the Editor, meeting abstracts, reviews, meta-analysis, in-vitro and animal experiments. Twenty articles with clinical results could be included. Most of the authors made attempts to correct for potential sources of bias by multivariate regression analysis or by propensity score analysis.

RESULTS

The following malignancies were under scrutiny: multiple myeloma [4, 5], endometrial [6, 7] and ovarian cancer [7], hepatocellular carcinoma [8,9], advanced prostate cancer [10, 11], non-small cell lung cancer stage IV [12], colorectal cancer [13, 14], lymphoma [15], renal cell carcinoma [16] and esophageal: squamous and adenocarcinoma [17]. Furthermore, transplantation related [18] and HIV related malignancies [19] were under scrutiny. Three manuscript dealt with malignancy in general and were based of asymptomatic persons who had purchased statins [20] or were in active military service [21, 22]. There were different approaches and designs. Six manuscripts were based on regional or national or insurance databases and national networks or registries [1, 4, 6, 8, 17, 20]. Five were case control studies [4, 7, 11, 13, 17]. There was at least four prospective cohort studies [6, 16, 18] and propensity analysis was used in several series [21, 12]. Some series has a specific design such as the PRIMA study, [15] or the phase I – open label comparison of different regimens of statins [23]. In one series, the effect of statins on survival in a specific group of patients who survived at least one year after cardiac transplant was described [18]. In another, HIV-patients were scrutinized [19].

Elimination of bias was attempted, mostly by regression analysis with inclusion of potential confounders [15] such as age, BMI, ethnicity, ASA class and oncologic parameters [7, 11, 16, 17]. In one manuscript, the focus was on blood lipid level as source of potential bias [4, 13]. In several series, statins were associated with metformin [8, 9, 21] or angiotensin-converting enzyme inhibitors [11,18]. Two major outcomes were studied: the effect of statin on overall or disease specific survival [5-7, 10-12, 15, 16, 18] and on cancer occurrence [4, 13, 17-21]. Few series addressed specific outcomes of statins such as the success rate of leukapheresis in patients with multiple myeloma [5] or the pathological response (according the American Joint Committee on Cancer grades) 0-1 v. 2-3 [5] and tissue score after radiotherapy [18]. These outcomes are shown in Table **1**, with the Odds ratios (or hazard ratio) and the 95% confidence interval.

DISCUSSION

The majority of the results indicated a favorable response of malignancy on statins, either in terms of disease progression and survival or on prevention, *i.e*. before the diagnosis of malignancy. This outcome has been observed for several malignancies as can be seen in the table.

The risk of multiple myeloma in population extracted from large database, could be reduced by 20-28% by long-term use of statins [4]. Progenitor cells in patients with multiple myeloma were more easily mobilized during leukapheresis by statins in patients who suffered from this malignancy [5]. The incidence of hepatocellular carcinoma in patients with hepatitis C viral infection and diabetes was reduced by metformin (but not by insulin) and cholesterol lowering medication [8], but this finding did not apply to all statin / metformin regimens [9]. Statins improved also the overall and disease-specific survival after surgery for renal cell carcinoma [16]. Long-term use of statins was inversely associated with the development of esophageal squamous cell and adenocarcinoma [17]. The use of statins reduced the incidence of endometrial cancer (but not ovarian cancer) and improved the survival after diagnosis for both types, even when statins were taken after diagnosis [7]. Median regression grade and response to neo-adjuvant chemo and radio in rectal

Table 1: Effect of Statins on the Outcome

Reference	Design	Cancer	Outcome	Result
Epstein 2017 (4)	Case control	Multiple myel	Prevention	20-28% reduction
Sanni 2017 (6)	Prosp. cohort	Endometrial	CSS	0.83 (0.64-1.08)
Kasmari 2017 (8)	Database	HCV/DM/AHT	HCC	0.65
Boegemann 2016 (10)	Retrospect	Prostate [meta]	PFS & OS	1.2 (0.4-4.2)
Lin 2016 (12)	Database	Lung stage IV	CCS OS	0.77 (0.73-0.81) 0.76 (0.73-0.79)
Mansi 2016 (22)	Retr. propens	Healthy	Malignancy	no effect
Mamtani 2016 (13)	Case control	Colorectal	Prevention	0.98 (0.79-1.22)
Bachy 2016 (15)	PRIMA study	Lymphoma	EFS & OS	no impact
Chen 2015 (9)	DM cohort +/- metformin	HCC	Prevention	0.32 (0.18-0.58) Simv 0.31 (0.19-0.52) Atorv 0.22 (0.08-0.61) Rosuv
Kaffenberger 2015 (16)	Retrospective	RCC-surgery	DSS OS	0.48 (0.28-0.83) 0.62 (0.43-0.90)
Galli 2014 (19)	Chart study	Ca in AIDS		0.45 (0.17-0.71)
Alexandre 2015 (17)	Database case control	Esoph (sq) (ad)	Prevention	0.58 (0.39 +/- 0.87) 0.29 (0.09 +/- 0.92)
Mace 2013 (14)	Retrospective	CRC	Lower grade after CT+RT	2.25 (1.33-3.82)
Lavie 2013 (7)	Case control	Ovarian Endometrial	Prevention Survival Prevention survival	0.56 (0.33-0.94) 0.47 (0.26-0.85) 0.59 (0.40-0.87) 0.45 (0.23-0.87)
Wedlake 2012 (23)	Prospective	Pelvic	GI-symptoms	"Reduced scores" 0.37
Marcella 2012 (11)	Case control	Prostate	Survival (unadj) (adj)	0.49 (0.34-0.70)
Lutski 2012 (20)	Database	All		0.69 (0.55-0.88)
Froehlich 2012 (18)	Prospective	After heart transplantation	Prevention	0.33 (0.21-0.51)

Ad: adenocarcinoma; adj.: adjusted; AHT: arterial hypertension; Ca: carcinoma; CSS/DSS: cancer/disease specific survival; CT: chemotherapy; DM: diabetes mellitus; esoph: esophageal; HCC: hepatocellular carcinoma; HCV: hepatitis C Virus; myel: myeloma; OS: overall survival; PFS: progress free survival; propens: propensity; retro.: retrospective; RCC: renal cell carcinoma; sq: squamous; RT: radiotherapy; unadj.: unadjusted; Ator / Rosuv / Simv: statines

cancer patients was improved by statins, but without improvement in oncologic outcome [14]. Statins with and without angiotensin converting enzyme inhibitors reduced digestive symptoms after pelvic radiation [18]. Statins in (otherwise asymptomatic) populations reduced cancer risk – especially hematopoietic malignancies [20-22]. Statins might decrease the rate of advanced prostate cancer and cancer mortality [11]. A favorable response was also documented in specific patient groups, with a suppressed immune system. Among HIV-1 treated patients, statin use was associated with a lower risk of cancer; the benefit was mainly related to AIDS-defining malignancies [19]. Furthermore, statins improved cancer free survival and overall survival in patients still living one year after heart transplantation [23].

Some series found no favorable effect. No effect of statins on the prognosis of follicular lymphoma was observed [15]. The "post-diagnostic" use of statins is not correlated with survival of endometrium carcinoma. This raises the question if and when there is an optimal time for administering statins for this purpose [6]. Statins associated with Abiraterone an androgen synthesis inhibitor did not improve survival in metastatic prostate cancer. This might be due to the fact that both drugs compete with one another for transport into the cell. This raises the question of potential pharmacodynamical interactions of statins with other drugs [10]. No differences with respect to malignancy have been observed in otherwise healthy persons, but some adverse effect such as an increase in diabetes was observed, without concomitant

cardiovascular beneficial effect [21, 22]. This indicates that statins should not be used without indication. It also raises the question of the duration of the treatment with statins. Of most interest, the risk of colorectal cancer was not significantly different among those who continued statin therapy and those who discontinued, but there might be an "indication bias": the increased serum cholesterol was inversely related to the risk for colorectal cancer. The collected data, however were considered incomplete by the authors and there could have been be residual confounding. An undiagnosed cancer might have a cholesterol lowering effect [13]. This indicates that the disentangling of the association of statins, the level of plasma cholesterol and malignancy is a difficult problem. Furthermore, the inflammatory status could complicate the matter further. Atherosclerosis is largely driven by inflammation, but for malignancy, this seems less clear cut. It seems that some modulation of inflammation is a precondition for malignancy to thrive. Either the cancer itself or its treatment might diminish the inflammatory response. In a larger autopsy report, an inverse correlation between malignancy and atherosclerotic disease was observed. This was corroborated in a second analysis, derived from the SHRINE database [1]. However, current results confirm an earlier meta-analysis comprising over 1,000,000 patients in 55 manuscripts that use of statins reduced significantly all-cause mortality (minus 30%), cancer specific mortality (minus 40%), progression free survival and disease free survival. This was consistent throughout stratification according subgroups (type of publication, type of malignancy, design of study, sample size, stage of the malignancy, duration of follow-up, area / country of study and initiation of statin treatment). Use of statins after diagnosis of cancer showed even a larger beneficial affect [24]. The current conclusion supports previous one that large scale prospective studies are needed. Prior as well as current approach are only hypothesis generating, while results from prospective studies are hypothesis confirming. The latter needs also a more sophisticated statistical approach since competing events are involved. In none of the included articles, except in one [19], a competing risk assessment according Fine and Gray has been performed. This has its importance in long-term studies of over 40 years, which are few in number [25-27]. However, some interesting observations have been made. Levels of cholesterol were inversely associated with colorectal cancer if the level of cholesterol was determined less than 6 months before the cancer diagnosis, but not if it was 24 months before this diagnosis. Statistical techniques such as propensity score analysis and instrumental variable analysis seems insufficient to solve the problem of indication bias [13]. An unexplained lowering of cholesterol could be a sign of occult colorectal cancer. This effect could be clouded by the use of statin, which can be considered as indication bias. Apart from the role of cholesterol, inflammatory status seems also to have an importance. This status is increased in atheromatosis, but decreased in cancer (especially with hematological malignancies), or by cancer treatment and in cachexia. Several interleukines and other inflammatory modulating hormones play an important role herein. It must be stated that these observations and theories were based on autopsy series [1]. In a specific subgroup of HIV patients, statins reduced the number of malignancies. Patients taking statins, however, were older than non-statin users and had more classical risk factors for cardiovascular disease and information about compliance was not available. In this view, statins had anti-inflammatory and anti-neoplastic activity while cholesterol – as important component of cell membranes played a role in the development of malignancy [19]. These reports indicate that there is no uniform view on the role of cholesterol. Furthermore, Kaplan-Meier analysis and Cox' proportional hazard analysis are insufficient if competing events such as cardiovascular or cancer death are under scrutiny. A Fine and Gray analysis has been proposed as alternative. Nevertheless, these methods become more important with the length of the follow-up, which is limited to 6 years for most of the currently included papers.

LIMITATIONS

The current manuscript addresses only clinical results. Papers concerning the intracellular mechanisms action of statins, as well as those of animal studies have been omitted. A meta-analysis has not been attempted because of the inhomogeneity of the studies. There is considerable variation in study design, sample size, tumor type, statin regimen (type, dose, timing) and measured outcome (reduction of potential malignancy v. survival after diagnosis of malignancy). Distinction between hydrophilic and lipophilic statins was not made. Current results confirm what has been observed earlier, but a large multicenter trial should be undertaken with inclusion of all possible confounders in order to disentangle the effects of cholesterol levels,

the changes of cholesterol levels and the effect of statins themselves. This is a major logistical endeavor. With current knowledge, ethical issues – withholding a potentially beneficial treatment – could hamper such enterprise.

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CONFLICTS OF INTEREST

None

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