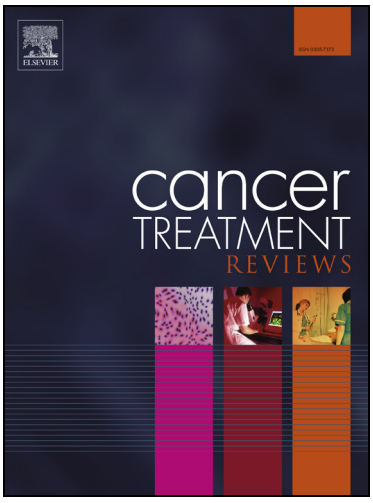

Controversy

The poor design of clinical trials of statins in oncology may explain their failure – lessons for drug repurposing

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The poor design of clinical trials of statins in oncology may explain their failure – lessons for drug repurposing.

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Running title: Deficiencies in clinical trials of statins

Abstract

Statins are widely used to treat hypercholesterolaemia. However, by inhibiting the production of mevalonate, they also reduce the production of several isoprenoids that are necessary for the function of small GTPase oncogenes such as Ras. As such, statins offer an attractive way to inhibit an "undruggable" target, suggesting that they may be usefully repurposed to treat cancer. However, despite numerous studies, there is still no consensus whether statins are useful in the oncology arena. Numerous preclinical studies have provided evidence justifying the evaluation of statins in cancer patients. Some retrospective studies of patients taking statins to control cholesterol have identified a reduced risk of cancer mortality. However, prospective clinical studies have mostly not been successful. We believe that this has occurred because many of the prospective clinical trials have been poorly designed. Many of these trials have failed to take into account some or all of the factors identified in preclinical studies that are likely to be necessary for statins to be efficacious. We suggest an improved trial design which takes these factors into account. Importantly, we suggest that the design of clinical trials of drugs which are being considered for repurposing should not assume it is appropriate to use them in the same way as they are used in their original indication. Rather, such trials deserve to be informed by preclinical studies that are comparable to those for any novel drug.

Keywords: Statins; Clinical trial design; Drug repurposing

Preclinical rationale for using statins in cancer patients

Statins are widely used to treat hypercholesterolaemia. They inhibit hydroxymethylglutaryl coenzyme A reductase (HMGCR) which is the rate-limiting step in the synthesis of mevalonate, a precursor for the biosynthesis of cholesterol (Fig 1). In addition to their role in controlling cholesterol, there is also a solid scientific rationale to consider repurposing statins for use as anti-cancer agents[1]. Mevalonate also is a precursor for the isoprenoids farnesol and geranylgeraniol which are used to post-translationally modify several small GTPase oncogenes (e.g. Ras, Rac, Rho). In several cases, this modification has been shown to be necessary for the correct subcellular localization of the small GTPases[2]. Consequently, statins provide an elegant way to inhibit these oncogenes, which otherwise have been considered by many to be "undruggable". HMGCR itself is recognized as a metabolic oncogene[3], and its expression is increased by gain-of-function variants of the commonly mutated tumour suppressor *TP53*[4]. It is abundantly clear from numerous studies from several groups (reviewed[5]) that, in laboratory studies, statins have desirable anti-cancer effects on a broad range of cell lines representing many cancer types. Statins induce G_1 cell cycle arrest and apoptosis in cancer cells *in vitro*[5]. Statins may be classified as lipophilic or hydrophilic. As anti-cancer agents, lipophilic statins are significantly more potent than hydrophilic ones, presumably reflecting their superior membrane permeability[6]. Indeed, one statin which is considered to be hydrophilic, pravastatin, is only weakly active against many cancer cell lines. Relatively high concentrations of even the lipophilic statins are needed to kill cancer cells but we have shown that statins used at these concentrations retain an "on-target" mechanism and affect cancer cells through inhibition of HMGCR[7].

Brief summary of the available clinical data

The widespread use of statins has created a rich source of data to perform retrospective analyses of the incidence of cancer and death from cancer in patients using statins to control hypercholesterolemia (reviewed[5]). Although some studies have reported a reduction in cancer-

related mortality among statin users, other studies have found no effect. This is perhaps not surprising because the dose and type of statin varies between patients and other factors which determine cancer outcome, e.g. health status, may not be adequately balanced between statin users and non-users. Most importantly, these patients have received statins at a dose and frequency that is designed to reduce plasma cholesterol, not to have an anti-cancer effect. Thus, it is not clear that such studies would detect an anti-cancer effect of statins, even it were present. Controlled prospective trials, designed to evaluate an anti-cancer effect, are required.

Table 1 summarizes 27 trials which have prospectively evaluated statins for the treatment of cancer. A minority of trials (8/27) included an arm in which the patients received a placebo. The trials have evaluated statins across a broad range of cancers, mostly solid tumours but activity in AML and multiple myeloma has also been explored. The majority of trials (19/27) have evaluated simvastatin or lovastatin, both of which are lipophilic. Relatively few trials (5/27) evaluated statins as single agents.

Two placebo controlled trials[8,9] showed an impressive 8-month increase in survival of patients with hepatocellular carcinoma, but the lack of widespread adoption of this into clinical practice over the intervening 10 years raises concerns about the validity of these observations. A further encouraging trial found that pravastatin combined with idarubicine and cytarabine led to a 75% response rate in relapsed AML with 20 of 26 patient achieving complete remission[10]. Apart from these trials, the remaining 23 trials have been significantly less successful and reported at best a mixture of partial response or stable disease in a minority of trial subjects. In particular, a recent placebo-controlled trial[11] evaluating pravastatin in 410 SCLC patients found no improvement in overall survival or progression-free survival.

Why have statins not been successful so far?

These data create a paradox – despite a robust preclinical data and some encouraging clinical studies, most prospective studies have been disappointing. We believe that this can be explained by three crucial factors that must be considered for the effective use of statins in cancer and that lack of consideration of these has led to the unsatisfactory design of many clinical trials.

Dose

Firstly, the concentration of drug required to cause cell death is significantly higher (10-fold) than that achieved in patients following the doses normally used to treat hypercholesterolaemia[12,13], suggesting that relatively high statin doses are necessary. This has also been recognized previously by several researchers, and 11/27 clinical trials employed a dose of statin that is significantly higher than that used to treat hypercholesterolaemia (Table 1). However, the majority of clinical trials evaluated a dose of statin that is appropriate to treat hypercholesterolaemia and which affords a plasma concentration of statins significantly below that required to induce apoptosis in cancer cells[12].

Schedule and choice of statin

Secondly, in laboratory studies, we have found that continual inhibition of HMGCR is necessary to induce apoptosis; *in vitro*, repeated daily cycles of 12 hours simvastatin interspersed with 12 hours no-drug did not induce apoptosis, whereas robust cell death was observed if the statin was continuously present[12]. This implies that in patients receiving short half-life statins (e.g. simvastatin, $t_{½}$=2-3 hr) once daily, HMGCR activity would recover between doses allowing resynthesis of isoprenoids and reactivation of small GTPases. A majority of clinical trials have used a dosing schedule that we consider to be inappropriate to treat cancer, instead apparently copying the schedule designed to treat hypercholesterolaemia. This problem is likely to have arisen in part for historical reasons. Lipophilic statins were developed before the hydrophilic ones and although they

are more potent in the cancer setting, they have a shorter metabolic half-life in patients due to their ready uptake into the liver and subsequent metabolism by cytochrome P450[14]. It is hard to conceive how such trials could ever work, now we know continual inhibition of HMGCR is necessary. The need to take into account the short half-life of lipophilic statins had been recognized by some researchers and 9/27 clinical trials increased the dosing frequency beyond that normally used to treat hypercholesterolaemia. A further two trials[15,16] used hydrophilic statins (atorvastatin, rosuvastatin) with relatively long half-lives that would improve drug exposure, but as we have noted above, these statins are less potent in a cancer setting.

Taking these two factors into account, a lipophilic statin with a relatively long half-life is desirable to allow potent and continuous inhibition of HMGCR. Pitavastatin is the only statin with this profile[17]. Its use is approved in the US and EU for hypercholesterolaemia but none of the clinical trials have evaluated pitavastatin in oncology.

Diet

Despite this understanding, our initial study evaluating pitavastatin against ovarian cancer xenografts in mice was unsuccessful[13], although others have reported that pitavastatin delayed growth of liver, colon and glioblastoma xenografts in mice[18-20]. We, and several others, have observed that geranylgeraniol can suppress the pro-apoptotic activity of statins *in vitro* suggesting that inhibition of the production of geranylgeraniol is likely to be essential for the anti-cancer activity of statin. This led us to consider whether isoprenoids might be found in mouse chow and human food and if this could impact the anti-cancer effect of statins. Solvent extracts of mouse chow, as well as human foods (rice, sunflower and olive oil) suppressed the pro-apoptotic activity of pitavastatin *in vitro*[13]. Literature data supports the existence of geranylgeraniol in these foods[21,22]. We subsequently found that pitavastatin caused regression of Ovcar-4 xenografts in mice maintained on a diet of Ensure Plus (a liquid human food replacement lacking isoprenoids)[13].

Strikingly, supplementation of the Ensure with geranylgeraniol restored tumour growth even though the mice still received pitavastatin. This suggests a third factor crucial to the effective use of statins - it may be important to eliminate isoprenoids from patients' diet. None of the prospective clinical trials of statins in cancer limited dietary intake of geranylgeraniol. In fairness, this is understandable as all the clinical trials we have assessed were conducted prior our report of the effects of dietary geranylgeraniol. However, it provides a further potential explanation for the failure of prospective clinical trials of statins in cancer patients.

Retrospective studies are unable to address these issues because these assess patients receiving a statin in a manner appropriate to control cholesterol, not cancer. To what extent patients received dietary advice which may have inadvertently limited geranylgeraniol is unclear. We suspect that the positive retrospective studies reflect an underlying anti-cancer activity of statins, which is more easily detected using the relatively large number of patients in these studies, possibly with a modified diet. Therefore, we consider it unlikely that retrospective studies will ever be able to uncover the full potential of statins in cancer. In our opinion, many prospective clinical trials of statins have been inappropriately designed and no single trial has adequately controlled all the variables necessary to evaluate the therapeutic potential for statins in oncology. Thus, there is a need for improved prospective clinical trials.

Proposals for the design of clinical trials design to improve the effect of statins in cancer

We suggest that pitavastatin is the statin most likely to be successful because of its unique combination of being both lipophilic and having a longer metabolic half-life. We suggest that clinical trials of statins should evaluate high doses of pitavastatin, given twice daily to maintain inhibition of HMGCR, while subjects are maintained on a diet which restricts their intake of isoprenoids such as geranylgeraniol. It is desirable to identify foods other than Ensure which lack geranylgeraniol to facilitate patient compliance with a restricted diet. It is noteworthy that several of the earlier trials

used a design comparable to that which we advocate – relatively high doses of statin administered several times during the day. However, these trials did not control diet and it is doubtful whether inhibition of HMGCR was maintained overnight because short half-life statins were used.

The high dose of statin we suggest mandates caution. Statins cause myopathy, which in the worst case can lead to rhabdomyolysis. Thus, careful dose escalation studies are necessary to determine if there is a therapeutic window for pitavastatin. It may also be useful to identify drugs (for example bisphosphonates[7,23] or dipyridamole[24]) which could potentially increase the therapeutic window by acting synergistically with pitavastatin.

It will also be important to discover predictive biomarkers that identify the patients most likely to respond to statins. Gain-of-function mutations in *TP53* can increase the expression of *HMGCR*[4], potentially providing one predictive biomarker. In addition, several groups have reported gene expression profiles that predict sensitivity to statins in cell culture studies[25-27]. These have included genes involved in the mevalonate pathway itself[26-28] and the epithelial-mesenchymal transition[25,29,30]. It seems appropriate that clinical trials of statins are designed to allow collection of tissue to consolidate these findings, or to identify additional biomarkers

Implications for repurposing of other drugs

These observations provide guidance for appropriate preclinical studies to assist the design of clinical trials for drug repurposing that can be applied to other drugs..

1. Simply transplanting the dosing regimen used in one disease and hoping that it will be applicable to another disease setting seems ill-advised. There is no reason to assume that the relationship between pharmacodynamic effect and efficacy is the same in two different diseases. In the case of statins, a 50% reduction in plasma cholesterol in low density

lipoprotein is clinically meaningful[31], but a similar inhibition of the mevalonate pathway may not be sufficient to kill tumour cells.

2. The dosing schedule that has been developed for treating the original disease may not be efficacious in another setting. Short half-life statins are effective at reducing plasma cholesterol if taken in the evening, because most cholesterol synthesis takes place overnight[32], but it is not clear that there is a similar pattern of geranylgeraniol synthesis in tumour cells. Preclinical studies to understand the relationship between exposure and efficacy in the new disease are essential to guide clinical trial design.
3. Different drugs from the same drug class may be behave similarly in one disease but differently in another. The differences in the pharmacodynamic and exposure requirements for efficacy between two diseases means that different drugs, even from the same drug class, may behave very differently in the new disease setting. For example, differences in half-lives or potencies between drugs may play a crucial role in determining whether they are efficacious in the new setting. In the case of statins, lipophilicity and a long half-life seem more important in oncology than in treating cardiovascular disease.
4. The patient population that will benefit from the repurposed drug needs to be defined. Statins are effective in the majority of patients with hypercholesterolaemia[33], but it does not necessarily follow that the majority of cancers are necessarily dependent on the mevalonate pathway.
5. There may be additional factors that affect the safety and efficacy of the drug in the new disease. For example, the supply of dietary geranylgeraniol may not impact the effect of statins on plasma cholesterol but it is likely to crucially affect their efficacy against cancer. Preclinical studies to identify such factors are appropriate prior to clinical trials. In the case of drugs which target metabolic processes, it seems sensible to evaluate the impact of diet on efficacy/safety and how this may be controlled in clinical trials.

We conclude that trials with statins in oncology have mostly been inadequately designed and the question whether statins are useful in the treatment of cancer remains to be properly addressed. We consider pitavastatin to be the statin most likely to be effective in cancer and appropriately designed clinical trials, following the guidelines we propose, are needed. In general, when drugs are being considered for repurposing, preclinical studies to understand how to use the drug are critical to support the diligent design of clinical trials.

Figure 1 Legend.

Figure 1. The mevalonate pathway. Statins inhibit the synthesis of cholesterol as well as isoprenoids needed for the function of several small GTPase oncogenes.

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AUTHOR CONTRIBTUIONS
All the authors contributed to the writing of the article and approved the final version.

CONFLICT OF INTEREST
The authors declare no potential conflicts of interest.

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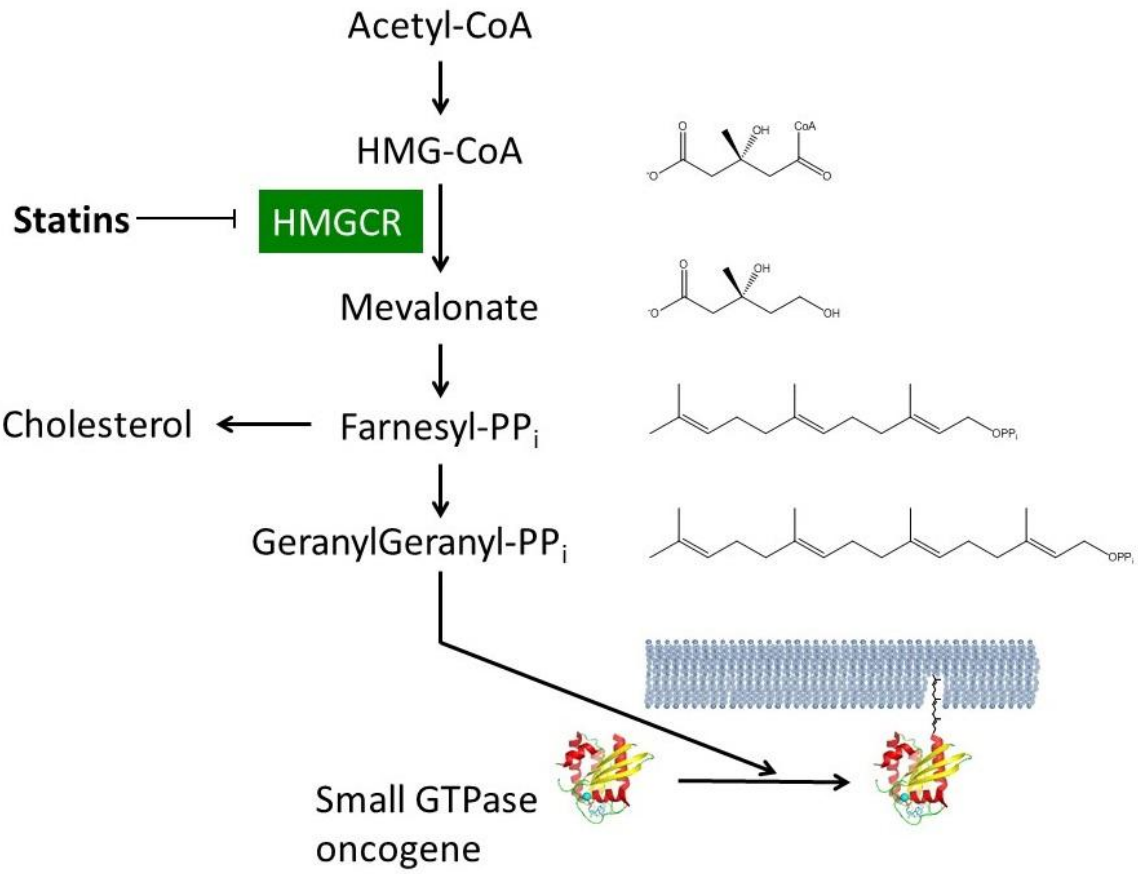

Cancer type	Statin	Concurrent therapy	Statin dose	Statin schedule	# patients	Response	Ref
Various	Lovastatin	N/A	2 to 45 mg/kg/day	4 x per day, monthly cycles of 7 days dosing	56	1 PR (2%)	[34]
Various	Fluvastatin	N/A	2 to 8 mg/kg/day	1 x per day, monthly cycles of 14 days drug,	12	2 PR (17%)	[35]
Gastric	Lovastatin	N/A	35 mg/kg/day	Split across 4x per day, 7 days, monthly cycles	14	1 SD (7%)	[36]
Hepatocellular carcinoma	Pravastatin	Prior TAE + 5FU	0 or 40 mg	1 x per day for 16 months	41 statin, 42 placebo	OS 19 months (Pravastatin) v 9 months (placebo) P=0.006	[8]
Head and neck squamous cell carcinoma	Lovastatin	N/A	5 to 7.5mg/kg/day	Explored several up to cycles of 21 days on, 7 days off, split across 4 x per day	22	6 SD (27%)	[37]
Various	Lovastatin	N/A	10 to 415mg/m^2	Every 6h, for 4 days, 24 days off, 1-6 cycles	32	4 SD (13%)	[38]
Myeloma, lymphoma	Simvastatin	Vincristine, doxorubicin, dexamethasone or cyclophosphamide, vincristine, doxorubicin,	5 to 15 mg/kg/day	Spilt across 2 doses for 7 days, prior to chemotherapy	28	1 CR (4%), 3 PR (11%), 3 MR (3%), 5 SD (18%)	[39]

		prednisolone.					
Myeloma, lymphoma	Simvastatin	Vincristine, doxorubicin, dexamethasone	15 mg/kg/day	Spilt across 2 doses, 2-4 cycles of 7 days on, 21 days off	12	1 PR (8%), 6 SD (50%)	[40]
Multuiple myeloma (chemotherapy resistant)	Simvastatin	Bortezomib, bendamustine	80 mg/day	Once daily, 5 days	6	5/6 (83%) show decreased paraprotein	[41]
Gastric	Pravastatin	TACE	0 or 20-40 mg/day	Once daily	131 TACE only 52 TACE & pravastatin	Increased OS 20.9 months (statin) versus 12 months (placebo) *P*=0.003	[9]
Brain stem tumours	Fluvastatin	Carboplatin, vincristine, thalidomide; radiotherapy	8mg/kg/day	1 x per day, 4 cycles of 28 days with statin days 1-14	9	7 PR (78%)	[42]
Multiple myeloma	Simvastatin	Various	15 mg/kg/day	Split across 2 doses, 2 cycles of 7days drug +21 days off	6	Study terminated early due to osteoclast activity	[43]
Colorectal	Simvastatin	Irinotecan, 5FU, leucovorin	40 mg/day	Once daily	49	Response rate comparable to historical studies of chemotherapy alone	[44]
Gastric	Pravastatin	Epirubicin, capecitabine, cisplatin	0 or 40 mg/day	Once daily	14 statin, 14 placebo	Response rate not increased by statin, study	[45]

						terminated before further accrual	
Non-small cell lung cancer	Simvastatin	Gefitinib	40 mg/day	Once daily	54 gefitinib & simvastatin, 52 gefitinb only	OS 13.6 months (gefitinib & simvastatin) v 12 months (gefitinib alone), P>0.05	[46]
Non-small cell lung cancer	Simvastatin	Irinotecan, cisplatin	40 mg/day	Once daily	56	42 PR (75%), 10 SD (18%) - not different to historical data	[47]
Pancreatic	Simvastatin	Gemcitabine	0 or 40mg/day	Once daily	58 gemcitabine & simvastatin 56 gemcitabine	1 year OS 27% (gemcitabine & simvastatin), OS 20% (gemcitabine alone) P>0.05	[48]
Colorectal (Kras mutant)	Simvastatin	Cetuximab, irinotecan	80 mg/day	Once daily	47	1 PR (2%), 33 SD (70%)	[49]
Acute myeloid leukemia	Pravastatin	Idarubicine, cytarabine	1280 mg/day	Once daily	36	20 CR (56%), 7 CRi (19%), significantly different from historical data P<0.05	[10]
Gastric	Simvastatin	Capecitaine, cisplatin	0 or 40 mg/day	Once daily	120 statin, 124 placebo	1 year survival 47.9 m (simavastatin) vs	[50]

						47.7 m (placebo)	
MDS	Atorvastatin	Idarubicin, cytarabine	1280 mg/day	Once daily	24	15 CR (63%), but didn't meet 70% CR rate criteria to continue study.	[16]
Colorectal (Kras mutant)	Simvastatin	Panitumumab		Once daily	14	1 (7%) patient durable PFS but didn't meet criteria to continue study.	[51]
Colorectal	Simvastatin	Irinitecan, leucovorin, 5FU or irinotecan, capecitabine	0 or 40 mg/day	Once daily	134 statin, 135 placebo	OS 15.9 m (simvastatin), 19.9 m (placebo), P>0.05	[52]
Colorectal (Kras mutant)	Simvastatin	Cetuximab	80 mg/day	Once daily	18	4 (22%) increased PFS but didn't meet criteria to continue study	[53]
Various	Rosuvastatin	Erlotinib	1- 2 mg/kg/day	Statin given daily 2 or 3 weeks; dose divided between and 4 times according to dose level.	22	4 (18%) SD	[15]
Brain metastases from various	Simvastatin	Radiation	0 or 80 mg/day	Once daily	50	1 year survival 8 % (statin),	[54]

tissue						vs 12% (control) P > 0.05	
Small cell lung cancer	Pravastatin	Etoposide + cisplatin or carboplatin radiotherapy	40 mg/day	Once daily	410 statin, 409 placebo	OS 10.7 m (statin), 10.6 m (placebo)	[11]

Table 1 A search of Pubmed for clinical trials containing the terms “statin” and “cancer” led to the identification of 27 reports. The table summarizes the type of cancer in which the statin was evaluated, the dosing regimen of the statin and the outcome. Trials which included a placebo arm are those in which dose is also reported as 0 mg/day. CR, complete response; PR, partial response; SD, stable disease; OS, overall survival; PFS, progression-free survival, TACE, transarterial chemoembolization.

Highlights

- Significant preclinical and retrospective clinical studies suggest statins are effective in cancer but prospective trials have failed
- Statin type, dose, dose interval, and patient diet have not been adequately considered
- An improved trial design for statins in cancer is proposed
- Clinical trial design during drug repurposing studies needs careful consideration.