JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Effects of Statins and Farnesyl transferase Inhibitors on the Development and Progression of Cancer

Dhvanir Kansara, Rajan Agrawal

L.J. institute of pharmacy, Ahmedabad, Gujarat, India

ABSTRACT:

Statins have been approved for the treatment of lipid disorders. Recently, in vivo studies with experimental animals and in vitro studies indicated a possible role for statins in the treatment of malignancies. Inhibition of the enzyme HMG-CoA reductase results in decreased farnesylation and geranylgeranylation of several proteins essential for cellular proliferation and survival. Inhibition of Ras farnesylation was originally thought to be the mechanism that mediates statin-induced effects in cancer. Consequently, specific inhibitors of the enzyme farnesyltransferase (FTIs) were developed. Currently, the mechanisms that mediate statin- and FTI-induced antitumor effects are questioned. It remains unclear which proteins and signal transduction cascades are involved. This review focuses on the effects and possible therapeutic application of statins and FTIs. Antitumor properties such as induction of growth arrest and apoptosis, inhibition of metastasis and inhibition of angiogenesis are discussed. Furthermore, the mechanisms of statin and farnesyltransferase inhibitor-induced effects and the involvement of a number of cellular components (such as farnesylated and geranylgeranylated proteins, the mitogen-activated protein kinase signalling pathway, the phosphoinositide 30-kinase signalling pathway, and cell cycle regulatory proteins) are reviewed. In addition, clinical and epidemiological data with respect to statins and farnesyltransferase inhibitors are summarised. It is proposed that inhibitors of the mevalonate pathway are particularly effective when administered in combination with other drugs. Therefore, the mechanisms and effects of combined therapy of statins or farnesyltransferase inhibitors with chemotherapeutics, biphosphonates, non-steroidal anti-inflammatory drugs, specific inhibitors of geranylgeranyltransferase and inhibitors of tyrosine kinase activity may be noticed in near future.

KEYWORDS: Statins; HMG-CoA reductase inhibitors; Farnesyl transferase inhibitors; Mevalonate pathway; Cancer

Article history:
Received 26 Jan 2014
Accepted 10 Feb 2014
Available online 13 Feb 2014

Non-standard abbreviations

AML	acute myeloid leukaemia	IGF-1R	insulin-like growth factor-1 receptor
bFGF	basic fibroblast growth factor	IPP	isopentenylpyrophosphate
Erk	extracellular signal-regulated kinase	MAPK	mitogen-activated protein kinase
Cdk	cyclin-dependent kinase	MMP	matrix metalloproteinase
COX-2	cyclo-oxygenase-2	Myr-Ras	myristilated Ras
EGF	epidermal growth factor	NOS	nitric oxide synthase
FTI	farnesyltransferase inhibitor	u-PA	urokinase-type plasminogen activator
FOH	farnesol	u-PAR	urokinase-type plasminogen activator receptor
FPP	farnesylpyrophosphate		
GGOH	geranylgeraniol	PDGF	platelet-derived growth factor
GGPP	geranylgeranylpyrophosphate	PI3K	phosphoinositide 3′-kinase
HMG-CoA	reductase 3-hydroxy-3-methyl-glutarylcoenzyme A reductase	PKB	protein kinase B
		Rb	retinoblastoma gene product

For Correspondence:

Mr. Dhvanir Kansara

L.J. institute of pharmacy, Ahmedabad, Gujarat, India

Email: dhvanir0410@gmail.com

(www.jpsbr.org)

INTRODUCTION:

3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors or ''statins'') are efficient and widely used drugs in the treatment of lipid disorders, especially hypercholesterolemia. The statin family comprises of lovastatin, simvastatin, atorvastatin, fluvastatin, and pravastatin. Although statins are approved only for the treatment of lipid disorders, there is increasing evidence that they may be useful in the treatment of other conditions, such as Alzheimer's disease[1–3] and osteoporosis. [4] Additionally, the potential of statins in the treatment of cancer has been investigated extensively in the last decade. The mechanism of action of this class of drugs is considered to be inhibition of HMG-CoA reductase, which is an enzyme up streaming the mevalonate biosynthetic pathway. HMG-CoA reductase catalyses the conversion of HMG-CoA into mevalonate. [5] An important intermediate of the mevalonate pathway is farnesylpyrophosphate (FPP; C15), an unsaturated carbon chain. Mevalonate can be converted into FPP in a number of steps. FPP is a precursor of several products of the mevalonate pathway, such as cholesterol, heme A, dolichols, and ubiquinones. In addition, geranylgeranylpyrophosphate (GGPP; C20) can be synthesised from FPP. Both FPP and GGPP are essential for the activation of a variety of intracellular proteins. In this activation step, the farnesyl or geranylgeranylmoieties are coupled to the protein, resulting in a farnesylated or geranylgeranylated protein. These reactions are catalysed by farnesyltransferase and geranylgeranyltransferase, respectively. This type of protein activation is referred to as (iso) prenylation. Several proteins involved in signalling are dependent on prenylation for their activity, such as Ras, nuclear lamins, transducin c, rhodopsin kinase, Rho, and all of the remaining heterotrimeric G proteins and small G proteins. [6,7] Most research has been focussed on statins and FTIs rather than GGTIs. Although inhibition of Ras farnesylation was originally considered to be the mechanism responsible for possible antitumor properties of statins and FTIs, there is increasing evidence that other mechanisms are involved as well. This review focuses on the potential therapeutic application of statins in cancer. Antitumor properties of statins and the mechanisms involved, such as induction of growth arrest and apoptosis, and inhibition of metastasis and angiogenesis, is discussed and an overview of clinical and epidemiological data on the incidence of cancer in users of statins are presented.[8]

Mechanisms of statin-induced cytostasis and cytotoxicity

The mechanisms of statin-induced effects on cell proliferation and induction of apoptosis are not yet fully understood. Several products of the mevalonate pathway, such as cholesterol, dolichol, ubiquinone, and isoprenylated proteins, have been evaluated as possible key compounds in the mechanism of statin-induced cytostasis. Although inhibition of protein prenylation has been generally accepted as an important mechanism for statin- induced effects, other intermediates of the mevalonate pathway have been suggested as critical compounds in statin effects as well.[9] Siperstein and Fagan observed a lack of negative feedback control in cholesterol synthesis in hepatomas and proposed that there was a relation between loss of cholesterol synthesis control and carcinogenesis. Several observations support this hypothesis. Impairment or complete loss of the cholesterol negative feedback has been observed in various types of cancer cells.[9, 10] Furthermore, cancer cells seem to require increased levels of cholesterol and cholesterol precursors. Recently, it was shown that statin-induced neuronal cell death could be prevented by treatment with cholesterol, indicating that the viability of these neuronal cells is dependent on cholesterol levels rather than non-sterol isoprenoids. However, cholesterol was not effective in prevention of statin-induced growth arrest or cell death in various other cell lines. Non-sterol isoprenoids may not be crucial for survival of neuronal cells because in contrast with most cells, neuronal cells do not divide.[11] The lack of DNA synthesis might provide an explanation for the discrepancy between neuronal cells and most other cell types. Furthermore, neuronal cells require higher amounts of cholesterol for membrane synthesis as compared to other cell types. The higher cholesterol requirement may provide an alternative explanation for decreased viability of neuronal cells caused by statin-induced cholesterol depletion. Another possible mechanism of statin-induced growth inhibition and apoptosis may be inhibition of dolichol synthesis. Dolichyl phosphate has a role in N-linked glycosylation of membrane proteins. It was shown that breast cancer cells were blocked in G1 by inhibition of HMG-CoA reductase and by specific inhibition of N-linked glycosylation by tunicamycin. Furthermore, tunicamycin decreased survival of Ewing's sarcoma cells. Moreover, N-linked glycosylation was shown to be down regulated in lovastatin-treated cells.[12] Particularly, N-linked glycosylation of insulin-like growth factor-1 receptor (IGF-1R) was decreased in association with decreased DNA synthesis. Although DNA synthesis was restored by addition of mevalonate, administration of both mevalonate and tunicamycin B prevented initiation of DNA synthesis. Addition of exogenous dolichyl phosphate up regulated IGF-1R expression in correlation with induction of DNA synthesis. These data suggest that inhibition of N-linked glycosylation contributes to statin-induced effects. However,

dolichyl phosphate was found to be unable to reverse statin-induced effects on cell growth in other studies and therefore, this mechanism is probably not a critical step in statin-induced growth inhibition.[12, 13]

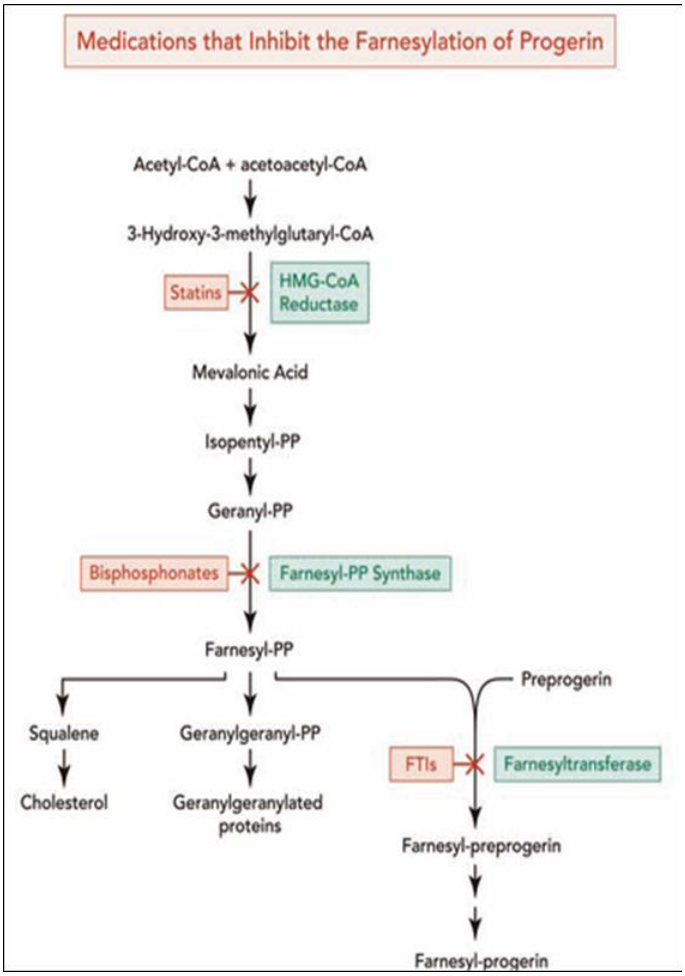

Figure 1 Targets of HMG-CoA, Bisphosphonates and FTIs

Farnesyltransferase inhibitors-

Preclinical and clinical studies since the effects of statins were considered at first to be mediated by inhibition of Ras farnesylation, specific inhibitors of farnesyltransferase have been developed. Various FTIs are available: manumycin, R115777, SCH66336, L744, BMS186511, RPR115135, SCH56582, and BIM46228. R115777 and SCH66336 are currently referred to as Zarnestra and Sarasar, respectively. FTIs induce reversion of morphological changes induced by Ras, block anchorage-independent growth and induce apoptosis in vitro. Studies revealed that FTIs block growth of both solid and non-solid tumours with little toxicity. Dose-limiting toxicities are gastrointestinal toxicities (nausea, diarrhoea, vomiting), renal insufficiency, dehydration, fatigue, neuropathy and myelosuppression (neutropenia and thrombocytopenia). The recommended dose is 500 mg twice a day, when R115777 was administered to patients with solid therapy with R115777 resulted in a recommended dose of only 300 mg twice a day. Importantly, 29% of acute leukemic patients responded to R115777 therapy, indicating that R115777 should be particularly investigated in myeloid leukemic patients. Effectiveness of farnesyltransferase inhibition by SCH66336 was shown by the dose-dependent inhibition of farnesylation of prelamin A in buccal mucosa cells of SCH66336-treated patients. Likewise, farnesyltransferase activity, lamin A farnesylation, and HDJ-2 farnesylation were shown to be decreased in bone marrow cells of R115777 treated patients. Unfortunately, R115777 did not demonstrate clinical activity in phase II studies with non-small-cell lung cancer patients and metastatic pancreatic cancer patients. In conclusion, these clinical studies suggest that FTIs may have therapeutic value in the treatment of some cancer types.[14]

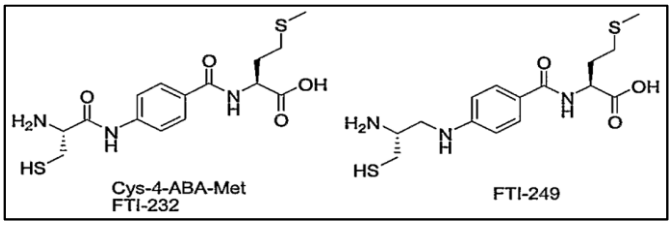

Figure 2 Structure of FTI-232 and FTI-249

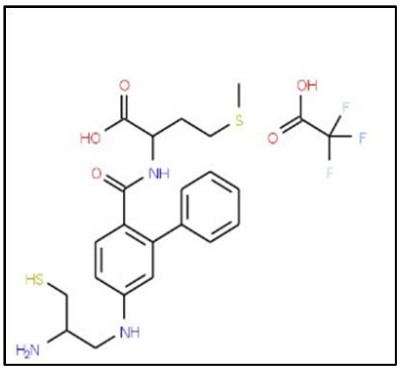

Figure 3 FTI 276 Triflouro Acetate

It costs around 122$ in USA market for 1 mg not for diagnostic purpose but for research only

RAS PROTEINS-

Initially, FTIs were designed to block Ras farnesylation. Indeed, several observations suggest that FTI induced effects are mediated by the Ras protein. Cells expressing Ras-F are sensitive to FTI treatment but cells expressing either myr-Ras or Ras- GG were not affected by FTI treatment. Another finding that suggests that FTI-induced effects are mediated by Ras inhibition, is that cells activated downstream of Ras, such as Raf-transformed and MEK-transformed cells, are hardly susceptible to FTI treatment.[15]

Overview of phase I trials with the FTIs SCH66336 and R115777

FTI	Tumour	Scheme	No. of patients	Dose-limiting toxicities	Other toxicities	RD[a]	RS[b]
SCH66336 (Ref. 213)	Solid	25–400 mg 2 dd 7 days	20	Gastrointestinal toxicities, fatigue, renal insufficiency, dehydration	Myelosuppression	350 mg 2 dd	PR[c]: 1 SD[d]: 8
SCH66336 (Ref. 211)	Solid	25–400 mg 2 dd Continuous	24	Gastrointestinal toxicities, fatigue, renal insufficiency, dehydration, myelosuppression, neuropathy	Anemia, fever, mucositis	200 mg 2 dd	SD: 2
SCH66336 (Ref. 309)	Solid	300–400 mg 1 dd 28 days and longer	12	Gastrointestinal toxicities, uremia, asthenia, myelosuppression	Upper gastrointestinal symptoms, abdominal symptoms	300 mg 1 dd	PR: 0 CR: 0
R115777 (Ref. 310)	Solid	25–1300 mg 2 dd 5 days	27	Neuropathy	Fatigue, renal insufficiency, hematopoietic toxicity	500 mg 2 dd	SD: 8
R115777 (Ref. 214)	Acute leukaemia	100–1200 mg 2 dd 21 days	34	Neuropathy	Myelosuppression, gastrointestinal toxicities, renal insufficiency, polydipsia, paresthesia	600 mg 2 dd	CR[e]: 2 PR: 8
R115777 (Ref. 311)	Solid	50–500 mg 2 dd Continuous	28	Myelosuppression, neuropathy	Gastrointestinal toxicities, fatigue, exanthema	300 mg 2 dd	PR: 1 SD: 3
R115777 (Ref. 312)	Chronic myeloid leukaemia	600 mg 2 dd 28 days 14 days rest	16	Fatigue, skin rash, peripheral neuropathy, myelosuppression	Gastrointestinal toxicities, pain, elevated transaminase/bilirubin levels, elevated creatinine levels	None	PR: 2 CR: 5
R115777 (Ref. 313)	MDS[f]	300–450 mg 2 dd 21 days 7 days rest	21	Myelosuppression, fatigue, myalgia, confusion	Rash, gastrointestinal toxicities, pain, elevated bilirubin levels, elevated creatinine levels, visual changes, headache	400 mg 2 dd	PR: 5 CR: 1

[a] RD, recommended dose.
[b] RS, response.
[c] PR, partial response.
[d] SD, stable disease.
[e] CR, complete response.
[f] MDS = myelodysplastic syndrome.

RHO PROTEIN

RhoB has been suggested as an alternative for Ras as a critical mediator of FTIs. It is a low molecular weight GTPase that can be both farnesylated and geranylgeranylated FTI treatment results in decreased levels of RhoB-F whereas levels of RhoB-GG are increased. In addition, the intracellular localisation pattern of RhoB is changed223 and growth stimulatory functions of RhoB are attenuated. Several observations argue for RhoB as a critical target of FTI action. RhoB has a relatively short half-life (approximately 2 h), indicating that in contrast to Ras-F, RhoB-F could be depleted when FTI-induced morphological changes towards a less neoplastic phenotype are completed Arguments against RhoB as key mediator of FTI induced reversion of malignant transformation are summarised by Sebti and Hamilton. Both RhoBF and RhoB-GG inhibit anchorage-dependent and anchorage-independent growth, induce apoptosis, and suppress tumour growth in nude mice, indicating that RhoB-F is not a critical target for FTIs.[15]

INVOLVEMENT OF PROTEINS THAT REGULATE THE CELL CYCLE-

The tumour suppressor gene p53 is largely dispensable for FTI-induced apoptosis and growth inhibition in vitro. However, a single molecular marker could not be identified that accurately predicted FTI sensitivity. Sepp-Lorenzino and Rosen254 investigated FTI-sensitive cancer cell lines and concluded that FTI treatment regulates p21 in a p53-dependent manner and that the Cdk inhibitor p21 is required for growth arrest. In the absence of p53 and p21, FTI-induced growth arrest was annihilated and apoptosis was induced. These results demonstrate that p53 and p21 may have a role in FTI-mediated effects, but the effects of these proteins are highly cell line-specific. FTIs have been shown to inhibit growth of a variety of human cancer cell lines in preclinical studies.[16]

Combinations with chemotherapeutics-

An overview of in vitro experiments with combinations of chemotherapeutic agents and statins or FTIs is presented in able. Several combinations were found to be more efficacious than monotherapy. These results have been confirmed in in-vivo experimental models. The effectiveness of combinations of either statins or FTIs and cytotoxic agents is highly dependent on the cell line, the cytotoxic agent, and the sequence of administration. The combination of cisplatin and the FTI SCH66336 was synergistic in non-small-cell lung cancer cells and glioblastoma cells, whereas antagonism was observed in breast, pancreatic, and colon cancer cell lines.[17]

COMBINATION WITH NSAIDs

Clinical, experimental, and epidemiological data suggest that NSAIDs have antitumor potential, particularly in cancers of the gastrointestinal tract. Some findings indicate that inhibition of cyclo-oxygenase 2 (COX-2) is involved in the antitumor activity. However, COX-2-independent mechanisms such as down regulation of proto-oncogenes have been suggested as well. Consequently, combinations of NSAIDs with drugs blocking tumour growth signals may be effective in the treatment of cancer. Scientists investigated the combination of sulindac and lovastatin and reported that lovastatin enhanced sulindac-induced apoptosis in colon cancer cells. Moreover, in vivo experiments in rats indicated that combinational lovastatin and NSAID therapy enhances NSAID-associated chemoprevention. Additionally, cell growth was inhibited synergistically by lovastatin and the COX-2 inhibitor MF-tricyclic in two murine colorectal cancer cell lines and lovastatin-induced apoptosis was enhanced synergistically by the COX-2 inhibitor celecoxib in human colon cancer cells. Findings on the effect of statins on COX-2 expression are somewhat conflicting. In human aortic smooth muscle cells, treatment with lovastatin and mevastatin resulted in increased COX-2 expression. This effect was mediated by inhibition of Rho protein. Statin treatment down regulated COX-2 expression in primary human umbilical vein endothelial cells.[17]

COMBINATION WITH GGIT

Similar to statins, GGTIs have been shown to arrest human tumour cells in G0/G1 phase and reduce growth in mice. Furthermore, the combination of GGTIs with chemotherapeutic agents was shown to be more efficacious than monotherapy. In order to acquire a more complete inhibition of protein prenylation, the effect of the combination of FTIs and GGTIs was investigated. In different cancer cell lines, combinational treatment with FTI and GGTI induced markedly higher levels of apoptosis than with either FTI or GGTI alone. However, doses of GGTIs that are sufficient to inhibit Ki-Ras prenylation are lethal to mice when continuously infused for more than 24 h. In contrast, lethality did not associate with GGTI treatment. Because the degree of geranylgeranyltransferase inhibition of treated animals was not determined, may have used GGTI doses that cause only partial geranylgeranyltransferase inhibition. These observations indicate that GGTIs may have a narrow therapeutic window.[18]

COMBINATIONS WITH AGENTS THAT TARGET TYROSINE KINASE ACTIVITY

Tyrosine kinase activity is important in signal transduction cascades. The EGFR family consists of receptor tyrosine kinases that activate the Ras/MAPK and PI3K pathways resulting in cellular proliferation and survival. Four members of the EGFR family have been identified: HER-1 (EGFR-1; ErbB-1), HER-2 (ErbB-2), HER-3, and HER-4. It was shown that an EGFR autocrine loop contributes significantly to the Ras-transformed phenotype in rat intestinal epithelial cells. Accordingly, FTI-induced growth inhibition was enhanced by EGFR blockade and glioblastoma cells that overexpress EGFR are more sensitive to FTI treatment. Furthermore, EGFR inhibitors potentiate lovastatin-induced apoptosis in head and neck squamous cell carcinoma cells that express EGFR Recently, the non-receptor tyrosine kinase Bcr- Abl fusion protein was recognised to play a central role in the pathophysiology of chronic myeloid leukaemia (CML). Since this protein provides constitutive active tyrosine kinase, the tyrosine kinase inhibitor STI571 (currently referred to as imatinib mesylate) was investigated as a therapeutic agent in CML.305 Although, imatinib mesylate has been shown to have antitumor potential in leukaemia, treatment of the LAMA84 cell line resulted in the development of resistance to STI571-induced apoptosis. Combinational therapy may overcome mechanisms of resistance development. Indeed, it was shown that the combination of STI571 and FTI results in an additive inhibitory effect on leukaemia cell proliferation. Importantly, growth of chronic myeloid leukemic cells from patients with STI571 resistance was inhibited by the FTI SCH66336. It was shown that SCH66336 was able to restore STI571-induced apoptosis in otherwise resistant cells.[19]

COMBINATIONS WITH BIPHOSPHONATES

Biphosphonates are drugs that suppress bone resorption and are currently used in skeletal disorders, such as osteoporosis. Although the exact mechanism remains to be elucidated, bisphosphonates are believed to reduce osteoclast activity. Several nitrogen containing biphosphonates (N-BPs) inhibited rat liver squalene synthase. Pamidronate and alendronate, both N-BPs, are poor inhibitors of squalene synthase but these agents reduce sterol biosynthesis from mevalonate, indicating that they inhibit another enzyme of the mevalonate pathway. Using crude enzyme preparations from bovine brain, N-BPs were shown to inhibit isopentenyl- PP isomerase, FPP synthase, or both. These results can be confirmed using rat liver cytosolic extracts and showed that recombinant human FPP synthase was inhibited by alendronate whereas purified rat liver IPP isomerase was unaffected. Other N-BPs were shown to inhibit FPP synthase as well and alendronate inhibited protein prenylation in osteoclasts and macrophages. NE21650, a novel N-BP that inhibits both FPP synthase and IPP isomerase, is more effective in inhibition of protein prenylation as compared with alendronate.[20]

Table 2

Effect of combinations of inhibitors of the mevalonate pathway and chemotherapeutic agents

Combination	Effect	Cell line
FTI SCH66336		
5-Fluoruracil	Antagonism	A-549, MCF-7, HCT-116, BxPC-3
Melphalan	Additive	A-549
Cisplatin	Synergism	A-549, T98G
Cisplatin	Antagonism	MCF-7, BxPC3, HCT-116
Paclitaxel, docetaxel	Synergism	MDA-MB-468, DLD-1, NCI-H460, PA-1, DU-145, LNCaP, AsPC-1, BxPC-3, MIAPaCa2, PANC-1
FTI L-744832		
Doxorubicin, cisplatin	Additive	MCF-7, MDA-MB-486
Vinblastin, 5-fluoruracil	Additive	MCF-7, MDA-MB-486
Paclitaxel	Synergism	MCF-7, MDA-MB-486
Lovastatin		
Cytarabin	Synergism	K-562, ARAC8D
Cisplatin, 5-fluoruracil	Potentiation	SW-480, HCT-116, LoVo, HT29
Sodium phenylacetate	Synergism	A172
Doxorubicin, radiation	Potentiation	HOS-AD5
Doxorubicin	Synergism	Colon-26
Doxorubicin	Additive	LLC, Ras-NIH-3T3
Sulindac	Potentiation	HCT-116, SW-480, LoVo
Manumycin A		
Paclitaxel	Synergism	ARO, DRO, KAT-14, KAT-18, C643, Hth-74
Cisplatin	Synergism	DRO, KAT-18
Doxorubicin	Synergism	KAT-4, Hth-74, C643
Simvastatin		
Cytarabin	Additive	HL-60, AML-2
Carmustin	Synergism	Human glioma cells
Cerivastatin		
Doxorubicin, cisplatin	Synergism	T4-2 breast cancer cells
5-Fluoruracil	Synergism	H630 and R10 colorectal cancer cells

CONCLUSION-

The antitumor properties of statins and FTIs have been extensively investigated. Growth arrest and induction of apoptosis have been observed in various cell lines. Additionally, inhibition of primary tumour growth and metastasis was shown in experimental animals. Unfortunately, evidence on the mechanisms that result in statin- or FTI-induced antitumor effects is rather conflicting. Possibly, mechanisms are not similar in different cell lines. Furthermore, chemoprevention and therapeutic effects may be mediated by different mechanisms. Prenylated proteins, such as Ras and Rho, have been shown to be involved in statin- and FTI-induced effects, but other proteins may be involved as well. Additionally, the contribution of downstream signalling cascades, such as MAPK and PI3K, requires further investigation. Many in vitro studies and in vivo studies have been performed using rodent fibroblasts or other rodent cells. The value of findings in these studies needs to be established in human (epithelial) cells. Clinical responses have not been observed in a phase II trial that investigated lovastatin monotherapy in patients with gastric cancer. However, combinations with other drugs may augment the statin-induced response, or may allow the use of lower doses. Several in vitro and in vivo studies confirmed that combinations of statins and FTIs result in additive or synergistic effects. Moreover, combination with other substances, such as biphosphonates, NSAIDs, GGTIs, and tyrosine kinase inhibitors, was shown to be beneficial as well. Further exploration of the combination of statins and FTIs with other compounds, such as chemotherapeutics, agents that interfere with the mevalonate pathway and agents that block other signal transduction cascades is needed.

REFERENCES

1. Simons M, Keller P, Dichgans J, Schulz JB. Cholesterol and Alzheimer's disease: is there a link. Neurology 2001; 57:1089–93.

2. Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. Lancet 2000;356: 1627–31.

3. Wolozin B, Kellman W, Ruosseau P, Celesia GG, Siegel G. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. Arch Neurol 2000;57:1439–43.

4. Coons JC. Hydroxymethylglutaryl-coenzyme A reductase inhibitors in osteoporosis management. Ann Pharmacother 2002;36:326–30.

5. Goldstein JL, Brown MS. Regulation of the mevalonate pathway. Nature (London) 1990; 343:425–30.

6. Casey PJ. Protein lipidation in cell signaling. Science 1995;268:221–5.

7. Rando RR. Chemical biology of protein isoprenylation/ methylation. Biochim Biophys Acta 1996;1300:5–16.

8. Bos JL. Ras oncogenes in human cancer: a review. Cancer Res 1989;49:4682–9.

9. Crick DC, Andres DA, Danesi R, Macchia M, Waechter CJ. Geranylgeraniol overcomes the block of cell proliferation by lovastatin in C6 glioma cells. J Neurochem 1998;70: 2397–405.

10. Vogt A, Qian Y, McGuire TF, Hamilton AD, Sebti SM. Protein geranylgeranylation, not farnesylation, is required for the G1 to S phase transition in mouse fibroblasts. Oncogene 1996;13:1991–9.

11. Ghosh PM, Ghosh-Choudhury N, Moyer ML et al. Role of RhoA activation in the growth and morphology of a murine prostate tumor cell line. Oncogene 1999;18:4120–30.

12. Jakobisiak M, Bruno S, Skierski JS, Darzynkiewicz Z. Cel cycle-specific effects of lovastatin. Proc Natl Acad Sci USA 1991;88:3628–32.

13. Keyomarsi K, Sandoval L, Band V, Pardee AB. Synchronization of tumor and normal cells from G1 to multiple cell cycles by lovastatin. Cancer Res 1991;51:3602–9.

14. Lee SJ, Ha MJ, Lee J et al. Inhibition of the 3-hydroxy-3-

methylglutaryl-coenzyme A reductase pathway induces p53-independent transcriptional regulation of p21waf/cip1 in human prostate carcinoma cells. J Biol Chem 1998;273:10618–23.

15. Macaulay RJ, Wang W, Dimitroulakos J, Becker LE, Yeger H. Lovastatin-induced apoptosis of human medulloblastoma cell lines in vitro. J Neurooncol 1999; 42: 1-11.

16. Rao S, Porter DC, Chen X, Herliczek T, Lowe M, Keyomarsi K et al. Lovastatin-mediated G1 arrest is through inhibition of the proteasome, independent of hydroxymethyl glutaryl- CoA reductase. Proc Natl Acad Sci USA 1999; 96:7797–802.

17. Wang W, Macauley R. Mevalonate prevents lovastatininduced apoptosis in medulloblastoma cell lines. Can J Neurol Sci 1999; 26:305–10.

18. Park C, Lee I, Kang WK. Lovastatin-induced E2F-1 modulation and its effect on prostate cancer cell death. Carcinogenesis 2001; 22:1727–31.

19. Van de Donk NW, Kamphuis MM, Lokhorst HM, Bloem AC. The cholesterol lowering drug lovastatin induces cell death in myeloma plasma cells. Leukaemia (Baltimore) 2002; 16:1362–71.

20. Weiss RH, Ramirez A, Joo A. Short-term pravastatin mediates growth inhibition and apoptosis, independently of Ras, via the signaling proteins p27Kip1 and P13 kinase. J Am Soc Nephrol 1999; 10:1880–90.