Statins in the treatment of polycythaemia vera and allied disorders: An antithrombotic and cytoreductive potential?

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Abstract

Thrombohaemorrhagic complications are major clinical problems in the classical chronic Ph-negative myeloproliferative disorders (CMPDs), polycythaemia vera (PV), essential thrombocythaemia (ET) and idiopathic myelofibrosis (IMF) [1–4]. In PV and ET thrombohaemorrhagic complications are the major determinants of morbidity [5]. High platelet counts in high risk patients of thrombosis and haemorrhage, hypermetabolic symptoms or symptoms of myeloid metaplasia (e.g. abdominal discomfort due to an enlarged spleen) have been conventionally treated with busulphan or hydroxyurea. Both drugs are potentially leukemogenic at least when being used sequentially in this patient group [6–8]. In younger patients alpha-interferon, PEG-Intron or anagrelide may be useful alternatives [9–13]. Since all these agents have side effects – and some even potentially leukemogenic – clinical trials are being conducted to find alternative and better drug formulations [14–22]. These pilot studies have included signal transduction inhibition (STI) with tyrosine kinase inhibitors (STI571; imatinib mesylate, Gleevec) [15–19] and inhibition of the enzyme farnesyltransferase in the mevalonate pathway [20–22]. Most recently, the farnesyl transferase inhibitor tipifarnib has been shown to preferentially inhibit in vitro autonomous erythropoiesis of PV patient cells implying that this treatment modality may be efficacious in PV [23].

In recent years, several studies have indicated that statins – besides a cholesterol lowering effect – possess anticancer properties as well by inhibition of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase upstream in the mevalonate pathway [24–41]. The statin family of drugs consists of those derived from fungal fermentation (pravastatin, simvastatin and lovastatin) and those which are fully synthetic (atorvastatin, fluvastatin, rosuvastatin, pitavastatin and cerivastatin (withdrawn from clinical use in 2001) [42,43]. Since statins besides antiproliferative, proapoptotic and antiangiogenic effects in addition have antithrombotic effects [44–53], including potential improvement of endothelial dysfunction [48,54–56] these agents may have a therapeutic potential in the CMPDs being featured by myeloproliferation, myeloaccumulation (decreased apoptosis), marked angiogenesis and an increased risk of thrombotic and haemorrhagic complications conse-
quent to platelet and endothelial cell activation/dysfunction [5,57–59]. Based upon in vitro and in vivo studies of the effects of statins (antithrombotic, antiproliferative, proapoptotic and antiangiogenic), this review focuses on the translation of these effects into potential clinical benefits of statin therapy in patients with CMPDs.

2. The mevalonate pathway

3-Hydroxy-3-methylglutaryl-coenzyme A reductase catalyses the conversion of HMG-CoA into mevalonate. This key enzyme is the rate-limiting step in cholesterol synthesis and the formation of isoprenoids such as farnesylpyrophosphate (FPP; C15) and geranylgeranylpyrophosphate (GGPP; C20) in the mevalonate pathway [60]. The enzyme is inhibited by statins giving rise to intracellular depletion of FPP and GGPP. Both intermediates of the mevalonate pathway are critical for activation of a variety of proteins involved in intracellular signaling. This activation step involves the transfer and subsequent binding of the farnesyl or geranylgeranyl moiety to the protein, resulting in a farnesylated or geranylgeranylated protein. This kind of protein activation involving the covalent attachment of hydrophobic isoprenoid molecules to target proteins is referred to as prenylation [61]. The processes are catalysed by farnesyltransferase and geranylgeranyltransferase, respectively. Prenylation is essential for membrane attachment and the subsequent participation of prenylated proteins in diverse signaling pathways regulating cell growth and survival [61–64]. Proteins that require farnesylation or geranylgeranylation for their function include guanosine triphosphate (GTP)—binding proteins such as Ras (farnesylation) [62–64] and the Rho family members Rac1 and RoA [65]. Accordingly, blockade of the mevalonate pathway may take place at several sites either upstream by inhibition of HMG-CoA reductase (statins), by inhibition of the activity of farnesyl pyrophosphate synthase (zolendronic acid and related amino-biphosphonates) and consequent depletion of FPP and GGPP or by direct inhibition of enzymes involved in the farnesylation of the proteins (farnesyltransferase/geranylgeranyltransferase inhibitors).

3. Antiproliferative and proapoptotic effects

During recent years the potential of statins in the treatment of haematological malignant diseases has been studied extensively [24–38,40]. As described above statins inhibit the prenylation of several important signaling proteins, including the Ras proteins. By inhibiting prenylation of Ras signal transduction in response to GF-stimulation the downstream activity in several important signaling pathways is inhibited with decreased proliferation and increased apoptosis [27,66–68]. The sensitivity of AML cells to statins appears not to be dependent on activating Ras mutations or overexpression and may also be dissociated both geranylgeranylation as well as farnesylation [34]. However, others have found that non-Ras geranylgeranylated proteins are important for statin-induced apoptosis of human AML cells [28]. Yet another mechanism responsible for the toxic effects of statins on AML cells seems to imply inhibition of intracellular cholesterol increments, which have been shown to be a protective cellular mechanism against injury [33,36]. Statins also profoundly modulate post-translational glycosylation of membrane targeted proteins consequent to depletion of dolichol. This compound is of major importance for the N-linked glycosylation of membrane targeted proteins. In particular, insulin and insulin-like growth factor (IGF) signaling appear to be disrupted, since the intracellular processing of these receptors requires dolichol for correct N-glycosylation, impairing the formation of intact and functional type 1 IGF and insulin receptors. Accordingly, deficient intracellular glycosylation of these receptors is followed by proreceptor retention within the endoplasmatic reticulum, prevention of their transfer to the cell membrane and consequently impairment of IGF-signaling and DNA-synthesis. Depletion of farnesyl pyrophosphate is also associated with impairment of mitogen signaling induced by both type 1 IGF receptor and the insulin receptor. Thus, HMG-CoA reductase inhibition and mevalonate depletion affects IGF and insulin signaling via at least two distinct but related and synergistic mechanisms: reduced prenylation of signaling intermediates such as Ras and disruption of the IGF and insulin proreceptor processing [69].

4. Angiogenic and antiangiogenic effects

Statins have biphasic effects on endothelial proliferation, high doses of statins inhibiting angiogenesis [55,56,70,71]. These biphasic actions may be explained by dose-related activation of different pathways. Thus, high dose effects have been shown to be related to inhibition of geranylgeranylation, whereas the low-dose effects were mediated by activation of PI3K/Akt pathway [55,71]. A proangiogenic effect has been shown to be associated with increased activity of endothelial nitric oxide synthase (eNOS) [54]. Other studies have shown that statins impair angiogenesis, being related to a different mechanism implying inhibition of RhoA [72,73]. It is tempting to speculate if the antiangiogenic effect may also be mediated by disruption of IGF-I signaling consequent to depletion of dolichol in endothelial cells, since IGF-I-in addition to directly stimulating angiogenesis [74] may also promote angiogenesis by stimulating the production of vascular endothelial growth factor (VEGF) [75,76].

5. Antithrombotic effects

Recently statins have been shown to exert direct cardiovascular effects, which are unrelated to cholesterol lowering [48,50,77]. As outlined above these include among others...
antithrombotic effects and effects upon endothelial function as well. In addition to a reduction in serum cholesterol levels, statins may also protect against thrombosis by decreasing platelet reactivity consequent to a reduction in the production of thromboxan A2 (TXA2) [78] or a reduction in the cholesterol content of platelet and erythrocyte membranes with ultimate decrease in the thrombogenic potential of these cells [77,79]. Furthermore, statins may decrease platelet activation by upregulating type III nitric oxide synthase in platelets [47], reducing circulating levels of sCD40 which are released from platelets upon activation [80] and together with other substances released from activated platelets, including IL-1beta [81] may elicit a prothrombotic state [82]. Furthermore, statins have been shown to reduce CD40 expression on vascular cells and circulating platelets [83,84] and inhibit CD40-ligand-dependent induction of COX-2 expression in endothelial cells by activated platelets [85].

Statins also decrease risk of thrombosis by increasing the vasodilatory, antithrombotic or inflammatory properties of the vascular endothelium by upregulating the enzyme generating nitric oxide (NO) (endothelial nitric oxide synthase) [54] with ensuing increased NO production from endothelial cells. The NO enhancing effect of statins is of major importance in their protective effect against atherothrombosis. The endothelium is preserved and NO also retards platelet aggregation and leukocyte adherence to the endothelium via the endothelial cell adhesion molecules, P-selectin and intercellular adhesion molecule-1 (ICAM-1) [86–88]. A similar vasculoprotective statin effect is also achieved by increasing COX-2 expression and prostacyclin PGH2 formation [89].

Statins may also decrease the risk of thrombosis by modulating coagulation and fibrinolytic pathways [90]. Thus, statins enhance the fibrinolytic activity within the vessel wall as reflected by the findings of reduced levels of plasminogen activator inhibitor-1 (PAI-1) and increased levels of tissue plasminogen activator (t-PA) within smooth muscle and endothelial cells [91]. Additionally, statins have been shown to inhibit tissue factor expression by monocytes and macrophages [77,92]. Statins also strongly enhance endothelial anticoagulant and fibrinolytic properties by increasing thrombomodulin expression and function in human endothelial cells [93].

6. Antiinflammatory effects

Statins have been shown to markedly attenuate leucocyte adherence to the endothelium being partly related to downregulation of endothelial adhesion cell molecules (i.e. P-selectin, ICAM-1) [86–88] but also to similar antiinflammatory effects upon leucocyte adhesion molecules with downregulation of CD11b (i.e. the alpha-chain of the beta2-integrins) and CD18 (i.e. the beta-chain of the beta2-integrins) [94]. All these antiadhesion molecule effects are dependent upon NO [88,94], and together they impair adherence of leucocytes to endothelium.

Statins also effectively lower plasma levels of C-reactive protein (CRP) [95,96] and increased CRP-levels have been shown to be predictive of an increased risk for coronary artery disease (CAD) in apparently healthy subjects [97–100]. Furthermore, the proinflammatory cytokines–tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), which stimulate CRP-production in the liver, are also decreased following treatment with statins [100,101]. This antiinflammatory effect may also positively influence the phenotype of the endothelium which otherwise in response to inflammatory mediators such as TNF-alpha and interleukin-1beta (IL-1beta) changes from a non-adhesive, non-thrombogenic cellular interface to one that expresses and secretes several adhesion molecules. Considering platelets as inflammatory cells statins accordingly have a combined antiinflammatory and antithrombogenic effect by decreasing circulating levels of sCD40 [80].

7. Discussion

Several of the effects of statins may be translated into clinical benefits to patients with CMPDs. First, statins have potent antiproliferative and proapoptotic effects and accordingly may decrease clonal myeloproliferation and accumulation of myeloid cells consequent to impaired apoptosis [24–27,33,35,36,40]. Second, in high doses statins have an antiangiogenic effect, which may be beneficial in these disorders as well [72,73,102]. Thus, endothelial proliferation in bone marrow and spleen is a prominent feature in the advanced myelofibrotic phase of PV and IMF [103–108]. In line with the development of bone marrow fibrosis the neovascularisation in the bone marrow and spleen is considered to develop consequent to the release of various growth factors from the megakaryocyte cell lineage including VEGF and bFGF [109,110]. Increased circulating levels of VEGF have been recorded in all three disease categories, being most pronounced in myelofibrosis patients [111–113]. Vascular endothelial growth factor is considered a key mediator of the abnormal angiogenesis in many other haematological malignancies [114,115] and is a survival factor for endothelial cells. It is intriguing to consider the possibility that VEGF may act as a growth and survival factor in CMPDs as well. If so, statins may interfere with the growth and survival promoting activity of VEGF as well as other important growth factors, including PDGF and bFGF [38,116–120]. Furthermore, statins through their antiproteolytic effect also decrease the release of several growth factors (e.g. VEGF, bFGF and TGFbeta) from the ECM of importance for cell proliferation, apoptosis and angiogenesis [121].

Besides the VEGF-system, the insulin growth factor system may be of particular pathogenetic importance in the CMPDs. The IGF-system consists of a family of insulin related proteins, including two growth factors (IGF-1 and IGF-2), their receptors (IGF-1R and IGF-2R) and various high-affinity binding proteins that regulate bioavailability and

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action of IGF [122]. Similar to VEGF’s, IGF’s are major proliferative/antiapoptotic cytokines and accordingly relevant therapeutic targets in several haematological neoplasias featured by enhanced proliferation and decreased apoptosis [123–125]. These growth factors promote cell proliferation and differentiation via specific receptors and are very important for erythropoiesis stimulating both erythroid and myeloid progenitor cells [122]. IGF-1 has an erythropoietin (Epo)-like activity that targets circulating early progenitor cells via an Epo-independent pathway [126] and most recently, IGF-2 has been shown to be a growth factor for haematopoietic stem cells [127]. The overproduction of red cells in PV has been explained by the combination of hypersensitivity of erythroid progenitor cells to IGF-I [128] and high circulating IGFBP-1 levels, the latter having a stimulating effect upon erythroid burst formation in vitro [129]. Recently, aberrant expression of IGF-2 has been described in Ph-chromosome negative CMPDs with a highly significant increase in IMF patients [130]. This observation further supports the concept of a significant role of this GF-system in CMPDs, being further underscored in the context of IGF-2 as a growth factor of haematopoietic stem cells [127]. Most recently, a major break-through in the molecular pathogenesis of the Ph-negative CMPDs has been described by the identification of a single point mutation (Val617Phe) in JAK2 in more than half of patients with CMPD being most prevalent in PV-patients (up to 97%) and present in about 50–60% of patients with ET and IMF as well [131–135]. JAK2 is a cytoplasmatic tyrosine kinase with a key role in signal transduction from multiple haematopoietic growth factor receptors [136]. Accordingly, the JAK2 mutation is thought to contribute to the sustained myeloproliferation and myeloaccumulation in the Ph-negative CMPDs.

Regarding the mevalonate pathway as a therapeutic target in the treatment of CMPDs and the IGF-system having an important role in sustaining myeloproliferation and decreased apoptosis it is of particular importance that interruption of the mevalonate pathway also profoundly affects IGF-signaling [69] and inhibition of IGF-signaling by mevalonate depletion may influence VEGF-signaling as well [137].

Comparative studies of the potency of the various statins in terms of their antiproliferative and proapoptotic effects have shown that the fungal-derived agents (pravastatin, simvastatin and lovastatin) have virtually identical antiproliferative properties on AML-cells [24–26]. The synthetic statins (cerivastatin, fluvastatin, lovastatin and atorvastatin) have all shown to be cytotoxic to AML cell lines as well but amongst them cerivastatin was found to be at least 10 times more potent in triggering apoptosis. Next to cerivastatin, the AML cell lines were most sensitive to fluvastatin, lovastatin and atorvastatin [29]. Since then cerivastatin has been withdrawn from clinical use due to an increased incidence of rhabdomyolysis. The differences in their proapoptotic potential may be related to different chemical, pharmacokinetic and pharmacodynamic properties. In particular, the degree of lipophilicity may be of importance determining the propensity of the drug to pass the cell membranes of neoplastic cells. Indeed, among the various lipophilic statins (cerivastatin, atorvastatin, simvastatin, lovastatin, fluvastatin and pitavastatin) cerivastatin has been shown to possess the greatest degree of lipophilicity [42,43] but also the most efficient statin to induce tumor-specific apoptosis [29]. On the contrary, among the hydrophilic statins (pravastatin and rosuvastatin), pravastatin has been found not to influence cell proliferation, which may be attributed to the hydrophilic nature of pravastatin and accordingly low penetration of the cells by the drug [41,43,44]. In the latter study human lymphoblast and myeloma cell lines were used, showing atorvastatin, lovastatin and simvastatin to possess almost identical cytotoxic effects, albeit the proapoptotic potential of atorvastatin and lovastatin was more pronounced than simvastatin [41].

Thrombosis and bleeding are frequent complications during the course of the CMPD’s. Besides abnormal rheology due to a raised haematocrit in PV-patients these events are primarily attributed to platelet and endothelial cell activation and dysfunction [5,57–59]. Other well-known risk factors for thrombosis in the general population – smoking, hypertension and diabetes mellitus – may further aggravate the thrombotic risk in these patients. Accordingly these risk factors are included in the risk-stratification of the individual patient when deciding the optimal treatment and when to start cytoreductive treatment [138].

Increased platelet activity has been found in several studies of patients with CMPDs [5] and is a well-known risk factor of acute coronary syndromes. In patients with hypercholesterolaemia, statins have been shown to decrease platelet activation being partly explained by lowering of plasma lipids. However, the antiplatelet effect also occurs independent of lipid lowering [77]. In patients with CMPDs, a direct antiplatelet effect of statins may be exerted by decreasing circulating levels of sCD40 [80] and accordingly also a CD40-mediated prothrombotic state [82–85]. Most recently, atorvastatin has been shown to reduce platelet activity by lowering the platelet-oxidized-LDL receptor expression in hypercholesterolaemic patients. Platelet deactivation occurred before significant LDL changes. Accordingly, the antiatherothrombotic action of atorvastatin was considered to be related to a cholesterol-independent reduction of the expression of a receptor molecule (oxidized-LDL) of utmost importance for platelet activation and development of thrombosis [139].

Endothelial activation and dysfunction has also been recorded in these patients as evidenced by increased plasma levels of the soluble adhesion molecule E-selectin (sELAM) and thrombomodulin [57,59] and a markedly impaired endothelial-dependent flow-mediated vasodilation [58]. The highest levels of sELAM were recorded in CMPD patients with thrombosis [57]. Thus, it has been suggested that dysfunctional endothelium with loss of its thromboreistant properties might also account for the increased risk of thrombosis in CMPD patients [57]. Statins may improve and restore endothelial function in CMPDs by stimulating endothelial nitric oxide synthase activity and consequently enhancing
NO production from endothelial cells [54,140]. Increased NO production also has an antithrombotic effect by impairment of both platelet aggregation and leucocyte adherence to the endothelium [87,102], the latter effect being elicited by downregulation of endothelial (P-selectin and ICAM-1) and leucocyte (CD11b and CD18) adhesion molecules [86–88,94,102]. Furthermore, statins also strongly upregulate endothelial cell thrombomodulin expression and activity thereby enhancing the anticoagulant and antiinflammatory properties of the vascular endothelium [93]. Recently, aspirin has been shown to reduce the risk of thrombosis in PV patients, but still a large proportion of the patients experience thrombotic events [141], which may not solely be attributed to platelet hyperactivity but also to elevated leucocyte counts and leucocyte activation [5,142]. The role of polymorphonuclear leucocytes in thrombogenesis has been recognized for several years [143]. Direct interaction of neutrophils and platelets are mediated through P-selectin (CD62P), which represents the first step in the formation of a leucocyte–platelet thrombus in vivo. Indeed, increased circulating platelet–leucocyte aggregates have been found in a significant proportion of patients with CMPDs being correlated with previous thrombosis, platelet activation and platelet count [144]. The statin fluvastatin reduces expression of P-selectin on platelets from hypercholesterolemic patients [88] and inhibit platelet–neutrophil interaction, this effect being mediated by inhibition of Rho-GTPases [145]. Based upon the observed alterations in platelet and endothelial function in patients with CMPDs and the above mentioned beneficial effects of statins upon platelet, leucocyte and endothelial interactions statins may certainly confer a protective role against thrombosis in CMPDs, in which increased thromboxan biosynthesis have been recorded in a large proportion of patients with PV [146,147]. The clinical benefits of statins may be evident even in patients receiving aspirin, reflecting that additional mechanisms other than those related to reduction in thromboxane are responsible [148]. Thus, statin therapy has been shown to reduce C-reactive protein levels independently of its effect on cholesterol [95,96]. A chronic low-level activation of the acute-phase response, either due to chronic inflammation, smoking, or biologically with increasing age is known to be associated with an increased long-term risk of atherosclerosis (angina pectoris), atherothrombosis (myocardial infarction) and death in the general population, even in persons with normal lipid levels [98–100,149]. Furthermore, statin therapy seems to be effective in the primary prevention of coronary events among persons with relatively low lipid levels but with elevated levels of C-reactive protein [150]. In addition, a reduced rate of progression of atherosclerosis is associated with intensive statin treatment [151]. Finally, persons with low CRP levels after statin treatment have been shown to have a better outcome than those with higher CRP levels irrespective of the resultant level of LDL cholesterol [152]. All these data provide a rationale for statin therapy of patients with CMPDs, at least in those with chronic, low-level activation of the acute-phase response as reflected in elevated C-reactive protein levels.

8. Conclusions and perspectives

Statins have potent antiplatelet and antiinflammatory effects, which together with restoration of endothelial dysfunction may decrease the risk of thrombotic complications in patients with CMPDs. In addition, statins have been shown to inhibit leukaemic cell proliferation, increase apoptosis of leukaemic cells and have demonstrated antiangiogenic effects. Given these observations a potential role of statins as cytoreductive and antiatherothrombotic agents in patients with CMPDs may be anticipated. If so, these effects may be further enhanced by combinational therapy with zoledronic acid, considering their different site of action within the mevalonate pathway [153].

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