STATINS IN CRITICAL CARE

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INTRODUCTION
Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are the most commonly used drugs for hyperlipidemia and for reduction in the risk of incidence of cardiovascular and stroke events. Recent data suggest that their effects go well beyond lipid lowering seen with long term use and may include acute inflammatory activity, anticoagulation, immunomodulation and promotion of changes in smooth muscle tone.

In view of this promising research has began into use of these agents in various critical areas, such as
1. Early phases of Sepsis,
2. Bacteremia,
3. In Ischemic Stroke,
4. Decrease in cerebral vasospasm after subarachnoid hemorrhage
5. Pulmonary Hypertension

ANTI-INFLAMMATORY EFFECTS

Statin therapy exhibit modulation of nitric oxide production by optimizing its availability in acute inflammatory states by suppressing vascular proliferative changes due to inflammation. Clinical biomarkers of inflammation such as C-Reactive proteins are also decreased by statins. Nitric Oxide (NO) is a potent local vasodilatory substance produced by vascular epithelium and necessary for optimal vessel patency and perfusion of variety of human tissue. Endothelial cells secret NO when exposed to sheer stress. High dose use of certain statins (Simvastatin 20 mg, Lovastatin 40 mg, Pravastatin 40 mg) has great arteriolar dilatation.

Statins also increases the amount of endothelial derived nitric oxide synthase (eNOs) within vascular endothelium subsequently increasing availability of nitric oxide. This increase of eNOs causes anti-inflammatory effects through inhibition of leukocyte & platelet adhesion also has decremental effect on inducible nitric oxide synthase (iNOs), as increase in iNOs causes inflammation that leads to neuronal cell death in ischemia & profound vasodilation in distributive shock.

In animal models simvastatin 50-100µgm/kg was shown to increase eNOS expression with decrease endothelial cell P-selectin expression by 50% within 18 hrs of administration. These regulatory actions on eNOS & iNOs result in statin serving potentially protective role in setting of acute inflammation by preserving balance of NO availability in vasculature.

Statins also appear to affect inflammation through antagonism of smooth muscle cell proliferation & immune cell recruitment. The adhesion molecules, vascular cell adhesion molecule-1(VCAM-1) & intercellular adhesion molecule (ICAM-1) are commonly associated with tissue damage & inflammation in setting of MI & stroke. Also VCAM-1 & ICAM-1 are downregulated by statins thereby blunting immune-mediated inflammatory response. Current data points to the fact that these effects of statins are largely independent of their lipid lowering ability.
IMMUNOMODULATORY EFFECTS

The influence of statins on immune function appears to be multifactorial. They not only influence chemokine production & decrease T-cell activation through inhibition of major histocompatibility class II antigen expression, but also decrease macrophage growth suppression and affect tissue factor. Its influence on tissue factor was demonstrated in a double blind placebo controlled parallel group study involving 20 healthy men (simvastatin 80mg/day v/s placebo for 4 days before giving iv lipopolysaccharide 20 IU/kg). Statin premedication inhibited increase of monocyte tissue factor expression after 4-8 hrs & decrease endotoxin induced formation of prothrombin fragment 1+2 demonstrating suppressive effect on inflammatory response to endotoxin.

Statins also interfere with endotoxin-induced leukocyte endothelial cell interactions leading researchers to ponder adjuvant role of these agents in treatment of infection.

ANTICOAGULANT EFFECTS

Due to the tight interrelation between the immune system, inflammatory response, and coagulation pathways the statins exhibit antiplatelet and anticoagulant properties. Statins affect coagulation by increasing platelet aggregation & adhesion through eNOS activity & direct inhibition of platelets. They also increase the activity of thrombomodulin and tissue plasminogen activator leading to anticoagulant effect. Studies have shown that atorvastatin & simvastatin increase transmembrane glycoprotein thrombomodulin expression which increases thrombomodulin-thrombin complexation leading to decrease in thrombin’s procoagulant potential and increase in activation of anti-inflammatory-anticoagulant protein C. The end result is that statins inhibit coagulation & promote fibrinolysis in setting inflammation, endothelial dysfunction & protein C deficiency.

ROLE OF STATINS IN ACUTE ILLNESS

Pulmonary hypertension

Rho-kinase activation is noted in models of pulmonary hypertension (PH). PH develops in rats exposed to hypoxia for 2 wks. Hypoxia induces p38 MAP kinase activation & proliferation of pulmonary fibroblasts. Studies have shown that this can be inhibited by statins. Chronic hypoxic therapy can be reversed by 2 wks therapy with simvastatin. Expression of rho-kinase 1 & 2 was markedly diminished in rats treated with simvastatin. Activity of rho-kinase increase three-fold under hypoxic conditions & normalized with simvastatin treatment.

Atorvastatin given daily for 4 wks decreases development of PH & decreases level of serotonin transporter protein in pulmonary vasculature. Pravastatin was able to significantly reduce PH & restore endothelium dependent relaxation. Both agents are able to restore endothelial nitric oxide synthase expression preventing apoptosis & improve medial wall thickening.

Open-label observational study at Standfort University Medical Centre, 16 pts with PH treated with simvastatin 20-80mg/day demonstrated improvement in 6 minute walk & cardiac output or decrease in right ventricular systolic pressure & improvement associated with simvastatin treatment. However further studies are required to validate the results.

ROLE OF STATINS IN ACUTE DISEASES

Bacteremia and Sepsis

In Bacteremia and Sepsis the statins act as inhibitors of leukocyte rolling, adherence & transmigration which has resulted in increased research into potential impact of statin therapy on infectious diseases.

Current information suggest that initial toxic stimulus such as bacteremia initiate cascade of events involving tumor necrosis factor & interleukin-1 that result in cell adhesion, clotting activation & overwhelming perpetuation of initial inflammatory & coagulation response leading to organ failure & increase mortality. Ability of statins to affect inflammation, coagulation & protein C activation & immune cell function may help to counteract this process. Several studies evaluating the effects of statins in sepsis and pneumonia were evaluated with disputed outcomes.

According to retrospective cohort studies evaluated between 1996 to 2007, showed that statin therapy compared with no statin therapy was associated with a 30% absolute reduction in the rate of severe sepsis. The rate of cardiovascular dysfunction, defined as hypotension requiring vasopressor therapy, was also lower in the statin group. Potential reduction in relative risk of mortality from sepsis by 16.6% compares favorably with some of most significant advancements in ICU care as early goal directed therapy. But hospital mortality was not significantly different between the two groups. However an article (Association between statin therapy and outcomes in critically ill patients: a nested cohort study) published on biomed central on 6th august 2011 showed that statin therapy was associated with a reduction in hospital mortality. This association was especially noted in high-risk subgroups.

However another recent article published in critical care medicine 2011 by Sachin Yende, Eric B et al showed that there were no differences in severe sepsis risk between statin users and nonusers for prior or continued statin use. There was a slight/modest increase in antithrombin activity over time in statin subject, with no difference in other coagulation, inflammatory, or lymphocyte cell surface markers. However further studies under the auspices of a randomized interventional trial of statin therapy, would be essential to confirm these preliminary observations.
CEREBRAL VASOSPASM

Subarachnoid haemorrhage accounts for 6-8% of all strokes & 22-25% cardiovascular deaths.

The presence of subarachnoid blood causes delayed vasoconstriction of cerebral arteries, increased production of superoxide anions & Fe++ ions after hemolysis which leads to increase levels of reactive oxygen species & increase binding of nitric oxide. Benefits of statins evidenced by attenuation of cerebral vasospasm & neurological deficit with 14 days of pretreatment with simvastatin have been observed.

ISCHEMIC STROKE

Statins can be used in ischemic stroke. Mechanism proposed is upregulation of eNOS leading to improved cerebral blood flow. High dose Atorvastatin 80mg/day has been shown to decrease rate of recurrent stroke or TIA in patients with no known history of CAD. When therapy was started within 1-6 months of initial event 5 year rate of recurrent stroke was reduced to 1.9% & that of cardiovascular events by 3.5% compared with placebo.

Larger cardiovascular study examining effect of high dose atorvastatin versus placebo started within 24-96 hrs after administration for unstable angina or non Q-wave MI was found to decrease in rate of stroke at 16 wks. Pleiotropic effect may extend from anti-inflammatory to immunomodulatory effects on vascular tone. Most of the published human studies are observational and retrospective, with the exception of those on cerebral vasospasm prevention.

DISCONTINUATION EFFECTS

Abrupt discontinuation of statins has shown to cause rebound effects & precipitation of consequences. Statin withdrawal results in suppression of eNOS production & leads to levels that are below baseline. The beneficial effect on platelet function & neuronal cell protection are nullified after withdrawal of statin therapy as soon as 2 days after discontinuation. Removal of these agents then amplifies developing effects of inflammation & coagulation resulting in increase in risk of ischemia, stroke & MI with worsening of clinical outcomes during acute illness.

Further investigations into the withdrawal of statin therapy needs to be pursued as cessation of therapy has been shown to rapidly (2-4 days) result in loss of protection against cerebral ischemia & thrombus formation.

One study reveals statin withdrawal result in increased mortality from bacteremia, as statin continuation decrease mortality.

Other study indicate that statin withdrawal may affect occurrence of vasospasm, demonstrating observational increase in delayed ischemic neurologic deficits after only 14 days of pravastatin 40 mg/day in previously statin-naive patients.

These data suggest that abrupt cessation of statin therapy might be of clinical concern & can have a negative impact.

CONCLUSION

At this time data do not warrant routine statin initiation in acute setting of bacteremia, sepsis, aneurysmal subarachnoid haemorrhage or ischemic stroke. Further prospective studies need to be conducted to firmly establish true effects statins may have in these acute processes. In contrast the data do seem to indicate that abrupt cessation of these agents, particularly in acutely ill patients may increase risk of adverse consequences. Therefore, unless harm will done by continuing therapy, it seems prudent for health care providers to take an active role in restarting & continuing these drugs.

REFERENCES