

Commentary

Statins, bugs and prophylaxis: intriguing possibilities

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Abstract

Statin therapy may represent a potential prophylactic intervention in certain high-risk scenarios, for example in pandemic influenza and in those undergoing aggressive medical treatments. Emerging data indicate a potential prophylactic role in these high-risk groups.

Introduction

Prophylaxis is defined as 'preventive treatment against disease'. A prophylactic measure that dampens the systemic response to infection or physiologic stress and has direct effects against the trigger of that response could greatly reduce the burden of illness associated with critical illness. Numerous clinical trials have provided unequivocal evidence that statins are safe and effective in preventing cardiovascular morbidity and mortality, and many statin-associated benefits are considered to stem from effects other than lipid modulation [1,2]. Intriguingly, observations indicate that statins may also directly affect the infectivity and proliferation of some microorganisms.

Viruses

Statins decrease viral loads and increase CD4⁺ cell counts in an *in vivo* model of acute HIV-1 infection [3]. Changes in Rho-controlled actin cytoskeleton rearrangements inhibit HIV-1 entry into and exit from host cells. Furthermore, many statins directly block the interaction between intercellular adhesion molecule (ICAM)-1 and leukocyte function-associated antigen (LFA)-1 by binding to a site within LFA-1 [4]. Consequently, the initial steps in virus replication can be limited. Moreover, six chronically HIV-1-infected, non-highly active antiretroviral therapy (HAART)-treated patients with stable viral loads for at least 6 months received lovastatin as sole therapy for 1 month [3]. Serum viral RNA loads were reduced in all patients, but they rebounded after lovastatin was withdrawn.

Statins also inhibit the replication of cytomegalovirus (CMV). Analysis of human umbilical-vein endothelial cells infected with CMV and co-incubated with fluvastatin demonstrate significant reductions in CMV DNA [5]. Viral particle concentrations are also lower. These effects are seen in doses consistent with blood concentrations *in vivo* observed during therapy in humans [6]. At high concentrations, lovastatin also strongly reduces hepatitis C virus RNA levels in cultured hepatoma cells and inhibits respiratory syncytial virus *in vitro* and *in vivo* in mice [7,8].

Bacteria and fungi

Lovastatin inhibits the sterol biosynthetic pathway in host cells containing *Salmonella typhimurium* and reduces the bacterium's intracellular proliferation in cultured macrophages [9]. Host cell death is implicated as a possible mechanism. Importantly, these effects were produced at plasma concentrations normally achieved during patient treatment. In the same study, mice were treated for 7 days with atorvastatin, then rendered septic by intraperitoneal injection of *S. typhimurium* and treated for a further 2 days after infection. Bacterial numbers in the livers and spleens of treated mice were reduced by more than 60%.

Ergosterol is the main sterol of fungal plasma membranes. The fungicidal polyenes and the fungistatic azoles are both directed against *Candida albicans* ergosterol. Micromolar concentrations of fluvastatin are fungicidal for *Candida* species [10]. In a recent study lovastatin reduced *C. albicans* gene expression, and consequently the organism's growth, by inhibiting the sterol pathway [11]. Synergism between lovastatin (5 µg/ml) and low concentrations of fluconazole was also observed.

CMV = cytomegalovirus; HAART = highly active antiretroviral therapy; ICAM = intercellular adhesion molecule; LFA = leukocyte function-associated antigen.

Potential implications

Although these findings must be confirmed, they raise several scientific and clinically important questions.

Do statins present a potential preventive and/or supplementary treatment for seasonal influenza and for the expected influenza pandemic?

Some viruses, notably H5N1, are highly potent inducers of a so-called 'cytokine storm' [12,13]. This excessive proinflammatory response contributes to the pathogenesis of severe influenza pneumonia and may partly explain the high mortality rates in young, otherwise healthy adults during the pandemic of 1918 to 1919 [13,14].

The immunomodulatory effects of statins occur through several pathways [15-17]. These include the direct activation of heme oxygenase, interference in leukocyte-endothelium interaction, and through inhibition of major histocompatibility class II complexes [4,18-20]. The most important, however, involves intracellular inflammatory signalling. GTP-binding proteins are crucial for intracellular inflammatory signalling by acting as molecular on/off switches for various protein kinases. They cycle between active and inactive states and must undergo isoprenylation to enable pathway activation. By inhibiting 3-hydroxy-3-methylglutaryl-CoA reductase, statins slow, but do not abolish, protein isoprenylation. This decrease in prenylated protein concentration reduces the response magnitude of the affected signalling pathways and may therefore counterbalance the influenza virus-associated 'cytokine storm' [15,16].

Considering these effects, the findings that statins also have direct antiviral effects, in some cases at physiologically relevant concentrations, raises the possibility that they may prove a valuable adjuvant therapy in the battle against seasonal and pandemic influenza, particularly in health systems unable to pay for expensive antiviral drugs or vaccines. The expected influenza pandemic represents a significant challenge to health care systems and to governments eager to avoid the potential human and economic consequences of large-scale infection and death. As things stand, the world is ill-prepared for a pandemic. Current world vaccine production capacity is only sufficient for a maximum of 450 million people to be vaccinated, and clinical trials of H5N1 vaccines have been disappointing [21]. Most of the world's people will therefore not have access to these vaccines.

Should patients at high risk of developing severe sepsis or septic shock receive 'prophylactic' statin therapy?

Early animal and human observational data suggest that statins may prevent sepsis and severe sepsis, and further data hint at a potential treatment effect [16,17]. Several observational studies specifically investigated the effects of statins in populations with infections or bacteremia [17]. Results again point to a preventive, and potentially a treatment, role.

Data indicate that a high proportion of patients presenting with systemic inflammatory response syndrome, infection or sepsis worsen to severe sepsis or septic shock. A recent study by Alberti and colleagues [22] provides data on the progression to severe sepsis and septic shock in patients admitted to ICU with an infection and/or sepsis: 11% of patients with infection and/or sepsis progressed to severe sepsis, whereas 13% progressed to septic shock. The overall crude hospital mortality rate was 41%. Hospital mortality rates ranged from 17% in those with sepsis without progression, to 97% in those who developed, and remained in, septic shock.

Patients who may benefit from prophylaxis are those admitted to hospital with an infection and who have a high likelihood of progression, or those placed at high risk by medical treatment. The latter group may include patients in whom bacteremia is expected, for example when non-sterile body cavities are opened (perioperative prophylaxis), or immunocompromised patients undergoing chemotherapy and those who have received solid organ or stem cell transplants (prevention of infections).

Statin therapy may represent a potential prophylactic intervention in certain high-risk settings. In view of the well-documented safety of statins, and the low cost of some preparations, research is needed to address these questions.

Competing interests

The authors declare that they have no competing interests.

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