COMMENTARY

Statins for sepsis?

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Statins inhibit the enzyme HMG-CoA reductase and thereby exert their well-known effect on cholesterol metabolism. In addition, statins may also exert anti-inflammatory, immune-modulating, and antioxidant effects, known as pleiotropic effects. The mechanism of action by which statins modulate the inflammatory pathways is complex and involves increased gene expression of NFκB, lowered expression of P-selectin influencing leukocyte-endothelium interaction, attenuation of up-regulation of Toll-like receptors and subsequent cytokine production, less platelet aggregation and less expression of tissue factor, less iNOS expression and augmented extracellular adenosine formation.[1,2] These effects raise the question if statins may play a role in the treatment of sepsis patients.

Several animal sepsis models have shown improved outcome with statin pre-treatment. It was also demonstrated that mice treated with statins six hours after a septic insult had improved outcome, although not as good as with statin pre-treatment.[3,4] In addition, there have been several observational studies that showed an association between statin treatment and improved outcome in humans. The largest of these observational studies was a cohort study from a Canadian administration database, with almost 70,000 patients.[5] There are two problems with these studies: First, their observational nature makes them prone to bias (for example, patients from a higher socioeconomic background are more likely to use statins and have a more beneficial prognosis compared with patients from a lower socioeconomic background) and second, the patients were already on chronic statin treatment and therefore no conclusions can be drawn on the acute effects of statins in sepsis patients. Over the past few years, several small, single-centre acute intervention studies were conducted. The ASEPSIS trial had fewer conversions from sepsis to severe sepsis in the atorvastatin group,[6] and in the HARP study,[7] the simvastatin group suffered less non-pulmonary organ dysfunction. However, these studies were too small to be able to detect effects on hard endpoints.

In April of this year, Kruger and co-workers published the first large, multicentre randomised trial that looked at the effect of a statin (atorvastatin) on intensive care patients with severe sepsis.[8] Patients already on statin therapy were also randomised, which meant that half of chronic statin users had to stop their statins. Patients had to be randomised within 48 hours of the start of their sepsis, and statins were continued for 14 days. The primary endpoint was the effect on interleukin-6 levels, as a measure of the immune response. Secondary endpoints were C-reactive protein concentrations, sequential organ failure assessment scores, intensive care unit (ICU) and hospital length of stay, and ICU, hospital, 28-day and 90-day mortality. The investigators found no differences between the intervention (n=123) and control (n=127) group in the course of interleukin (IL)-6 levels. The patients on chronic statin therapy had lower IL-6 concentrations, regardless of whether they were subsequently randomised to the statin or control group. There were no differences in the secondary endpoints between the two groups. In subgroup analyses, the patients on chronic statin therapy, who were randomised to the intervention group (so who continued statin therapy), had a lower 28-day mortality. As the survival benefit was only found in patients who were already on statins, while their IL-6 was similar to prior statin users who were randomised to placebo, these results suggest that the value of IL-6 as a marker of the statin effect is limited. In conclusion, this study suggests that initiation of statin therapy within 48 hours of the start of the SIRS response and treatment continued up to day 14 is not beneficial in sepsis patients. However, if a patient is already on statin therapy, the study suggests that when sepsis develops, continuation of statin therapy might be beneficial for the patient.

Preclinical pharmacodynamic experiments with HMG-CoA reductase blockers suggested that it could be the sepsis-wonder drug. Animal and observational studies also looked promising; however, once again, from evidence obtained in randomised prospective studies, the role of statins in sepsis appears to be limited. Larger multicentre prospective trials would be needed to demonstrate possible beneficial clinical effects and mortality advantages with the use of statins in septic patients. For now, continuation of statin therapy in a patient with sepsis could be recommended.

References

References: see page 25.