Why Did the Anti-C5 Complement Antibody Pexelizumab Not Reduce Infarct Size but Influence Clinical Outcomes Positively When Applied as Adjuvant Therapy to Primary Percutaneous Coronary Intervention?

To the Editor:

Mahaffey et al\textsuperscript{1} and Granger et al\textsuperscript{2} studied pexelizumab (Alexion Pharmaceuticals, Inc, Cheshire, Conn) as adjuvant therapy to fibrinolysis\textsuperscript{3} and to primary percutaneous coronary intervention (PCI)\textsuperscript{2} in acute myocardial infarction. Both groups obtained unexpected results: Mahaffey et al\textsuperscript{1} did not observe any positive action of pexelizumab, and Granger et al\textsuperscript{2} did not obtain any reduction of infarct size but did observe a substantial decrease in mortality.

It has been proposed that: (1) thrombolysis themselves are quick and powerful activators of complement\textsuperscript{4}; (2) thrombolysis transforms grossly visible anemic infarcts into hemorrhagic ones\textsuperscript{4}; (3) alleged erythrocytes in hemorrhagic infarcts are, in reality, cardiomyocyte apoptotic bodies\textsuperscript{4}; and (4) activated complement plays a decisive role in their formation.\textsuperscript{4} Using PCI instead of thrombolysis, Granger et al\textsuperscript{2} not only avoided a powerful activation of complement and a transformation of anemic infarcts into hemorrhagic ones, but they were also able to start pexelizumab treatment a median of 15 to 17 minutes before PCI. These were ideal conditions for this treatment and one would therefore expect a reduction of infarct size in the experimental groups. Nothing like that happened, however, and infarct sizes were not significantly different between all groups. The second surprise followed when the authors\textsuperscript{2} realized that pexelizumab had a positive influence on clinical end points, particularly mortality. Unfortunately, as in the study of the companion group,\textsuperscript{1} neither autopsies nor histopathological findings in the hearts of dead patients were presented, and we are limited to conjectures and hypotheses as to what really happened in the hearts of the enrolled patients.

We know from the outstanding article by Waller et al\textsuperscript{3} that grossly visible anemic infarcts have numerous foci of interstitial hemorrhage visible only with the microscope. The question, then, is whether these small hemorrhagic interstitial foci are composed of red cell or cardiomyocyte apoptotic bodies.\textsuperscript{3} The term infarct or infarction designates an area of necrosis from an insufficiency of blood supply. Consequently, there is not enough blood to create hemorrhages in such areas, and I favor the hypothesis that even small interstitial hemorrhagic foci in myocardial infarction are, in reality, cardiomyocyte apoptotic bodies.\textsuperscript{3}

A reperfusion by PCI activates complement but not so much as thrombolysis does. That is why we rarely see grossly visible hemorrhagic infarcts after such reperfusion. The reperfusion by PCI may, however, increase the number or dimensions of small interstitial hemorrhagic foci visible by light microscopy. Such an increase may be so small that it is beyond the sensitivity of the creatine kinase-MB assay or the creatine kinase-MB isoenzyme is not released into circulation from apoptotic bodies. In both alternatives, the infarct size remains the same in experimental and control groups, even if the protective action of pexelizumab takes place as evidenced by a decrease of adverse clinical outcomes, particularly by a reduction in mortality.

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4. Beranek JT. Why primary angioplasty is less offensive to the myocardium compared with thrombolysis for acute myocardial infarction. Am Heart J. 2000;140:e5.

Response

Dr. Beranek provides hypotheses as to why the mortality reduction with pexelizumab with primary percutaneous coronary intervention (PCI) in the COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA) trial was not accompanied by (1) an appreciable reduction in infarct size or (2) an accompanying effect in the parallel fibrinolytic-based COMplement inhibition in myocardial infarction treated with thrombolYtics (COMPLY) trial. Since the publication of the results of these trials,\textsuperscript{1,2} the pexelizumab for Reduction in Infarction and Mortality in Coronary Artery Bypass Graft surgery (PRIMO-CABG) trial results have been presented\textsuperscript{3} and provide further evidence of a benefit of pexelizumab in reducing death as well as myocardial necrosis in cardiac ischemia/reperfusion, in the setting of coronary artery bypass surgery.

We agree with his suggestion that there may be critical differences in the reperfusion process with primary PCI versus fibrinolytic therapy that could explain a difference in treatment effect of pexelizumab. Although the more abrupt restoration of flow (and embolization) with primary PCI or a different pattern of apoptosis may be relevant to these differences, the specific explanation remains speculative.

Although we hypothesized that a clinical benefit of pexelizumab would be evident through a reduction in infarct size measured by creatine kinase-MB release, the finding of dissociation has several possible explanations.\textsuperscript{4} We agree with Beranek that an impact on apoptosis, which is substantially reduced by pexelizumab in animal models,\textsuperscript{5} provides an appealing explanation for how clinical outcome might be improved without detectable changes in 72-hour creatine kinase-MB release.

Future clinical trials of pexelizumab and other agents aimed at modifying inflammation and other cellular mechanisms of the ischemia/reperfusion response will provide important opportunities to better understand novel pathways while defining the impact on clinical outcomes.

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