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

To the Editor:

Mahaffey et al1 and Granger et al2 studied pexelizumab (Alexion Pharmaceuticals, Inc, Cheshire, Conn) as adjunctive therapy to fibrinolysis3 and to primary percutaneous coronary intervention (PCI)4 in acute myocardial infarction. Both groups obtained unexpected results: Mahaffey et al5 did not observe any positive action of pexelizumab, and Granger et al5 did not obtain any reduction of infarct size but did observe a substantial decrease in mortality.

It has been proposed that: (1) thrombolitics themselves are quick and powerful activators of complement;6 (2) thrombolysis transforms grossly visible anemic infarcts into hemorrhagic ones;7 (3) alleged erythrocytes in hemorrhagic infarcts are, in reality, cardiomyocyte apoptotic bodies;8 and (4) activated complement plays a decisive role in their formation.4 Using PCI instead of thrombolysis, Granger et al2 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 authors2 realized that pexelizumab had a positive influence on clinical end points, particularly mortality. Unfortunately, as in the study of the companion group,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 al8 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.9 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.4

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.

Jiri T. Beranek, MD
4101 S. Wappel Dr
Columbia, MO 56203

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,1,2 the pexelizumab for Reduction in Infarction and MortalitY in Coronary Artery Bypass Graft surgery (PRIMO-CABG) trial results have been presented3 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.4 We agree with Beranek that an impact on apoptosis, which is substantially reduced by pexelizumab in animal models,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.

Christopher B. Granger, MD
Kenneth W. Mahaffey, MD
Duke Clinical Research Institute
Durham, NC

W. Douglas Weaver, MD
Henry Ford Hospital
Detroit, Mich

Pierre Theroux, MD
Montreal Heart Institute
Montreal, Quebec, Canada

Judith S. Hochman, MD
New York University School of Medicine
New York, NY
Correspondence

Thomas G. Filloon, PhD
Thomas G. Todaro, JD, MD
Procter & Gamble Pharmaceuticals
Mason, Ohio

Scott Rollins, PhD
Christopher F. Mojcik, MD, PhD
Alexion Pharmaceuticals, Inc
Cheshire, Conn

Jose C. Nicolau, MD
Heart Institute
University of Sao Paulo Medical School
Sao Paulo, Brazil

Witold Ruzyllo, MD
National Institute of Cardiology
Warsaw, Poland

Paul W. Armstrong, MD
University of Alberta
Edmonton, Alberta, Canada


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

Jiri T. Beranek

doi: 10.1161/01.CIR.0000127111.19811.F9

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/109/16/e195

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/