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Pexelizumab and survival in cardiac surgery

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ABSTRACT

A recent international consensus conference on the reduction in mortality in cardiac anesthesia and intensive care included pexelizumab, a recombinant monoclonal antibody to the component 5 of the complement system, among the ancillary (i.e. non-surgical) drugs/techniques/strategies that might influence survival rates in patients undergoing cardiac surgery. The consensus conferences state that "A subgroup analysis of a meta-analysis of randomized controlled trials suggested that pexelizumab might reduce mortality (longest follow up available, up to 6 months) in patients undergoing coronary artery bypass grafting. Pexelizumab was not included among the most important topics of the consensus conference as it was the only topic that did not receive a sufficient percentage of votes from the audience (32 % at the first round and 35 % at the second round). Pexelizumab is no longer on the market, however, the concept of reducing the generalized inflammatory process accompanying cardiopulmonary bypass deserves further investigation.

Keywords: *CABG surgery, mortality, inflammation, complement system*

The recent international consensus conference on the reduction in mortality in cardiac anesthesia and intensive care (1, 2) considered Pexelizumab among the drugs that could reduce mortality in cardiac surgery. Pexelizumab is a recombinant humanized single-chain monoclonal antibody to the component 5 of the complement system (C5). It blocks the C5 conversion into C5a and C5b. C5a is a powerful anaphylatoxin and proinflammatory mediator, and C5b is the precursor of "C5b-9", the Membrane Attack Complex (MAC). The latter is a transmembrane channel involved in thrombosis and inflammation, which also causes direct tissue injury through osmotic lysis (3). Pexelizumab administration on top of conventional treatment has been tested in ST elevation myocardial infarction (STEMI) and on-pump coronary artery bypass grafting (CABG).

In the STEMI setting, utility of Pexelizumab has been ruled out by the results of our systematic review and meta-analysis (4).

Conversely, within the same manuscript we suggested that Pexelizumab administration in patients undergoing CABG surgery could significantly reduced the relative risk of all-cause death by 26 %: (OR 0.74 [0.5-0.94], P = 0.01) with a number needed to treat of 100 (95 % CI 33-167).

The lack of benefit of Pexelizumab in the setting of patients with STEMI clearly contrast with the apparent benefit observed in patients undergoing CABG. In other words,

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the diverse effect of Pexelizumab might reflect crucially important differences of the two settings in which it has been tested. Indeed, in animal models of tissue reperfusion injury (common in STEMI setting) an increased accumulation of MAC (C5b-9) was demonstrated as well as quite stable levels of C5a during cardiopulmonary bypass (5, 6).

Conceivably, in the setting of STEMI once microvascular damage and myocardial death due to necrosis, ''local'' inflammation, and apoptosis have become irreversible, complement activation could have already led to MAC formation, thus nullifying any benefit from Pexelizumab. Furthermore, penetration of Pexelizumab into myocardial tissue may be limited as a consequence of microvascular obstruction and local metabolic derangement.

On the other hand, upstream administration of Pexelizumab could reduce the ''generalized'' inflammatory process accompanying cardiopulmonary bypass.

When considering the unconvincing evidences and knowledge of its beneficial effect, it doesn't surprise that Pexelizumab is no longer on the market and only 32 % to 35 % of the participants to the Consensus Conference included it among the life-saving drugs in cardiac surgery. The discouraging results of Pexelizumab led to the end of the drug, not to the end of the concept, perhaps the way to an effective antinflammatory/anti-complement drug should probably start from a better knowledge of the underlying mechanisms of such an innate immune response in patients undergoing CABG, and then on possible preventive strategies which might positively affect the outcome.

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