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# The mechanism of action of the adrenomedullin-binding antibody adredezumab

Christopher Geven<sup>1,2</sup> and Peter Pickkers<sup>1,2\*</sup> 

See related review by Levy et al., <https://ccforum.biomedcentral.com/articles/10.1186/s13054-018-1967-3>

With interest we read the review by Levy et al. [1] that provides a thorough overview of current and future therapies aiming to treat vasoplegia, an ubiquitous phenomenon in shock. In their work, the authors dedicated a section to the novel adrenomedullin (ADM)-binding antibody adredezumab, which is mentioned as an *ADM blocking* compound in the section title. Recently published studies demonstrate that blocking of ADM does not accurately describe adredezumab's mechanism of action, though.

In contrast to what is often intuitively assumed, not all antibodies completely inhibit the activity of their targets. The extent of signaling inhibition can vary greatly, depending on the epitope to which the antibodies bind and other factors, such as antibody concentrations. In contrast to C-terminus binding anti-ADM antibodies which completely inhibit ADM signaling, antibodies against the N-terminus of ADM, including the humanized monoclonal antibody adredezumab, only *marginally* inhibit ADM activity, despite their high affinity and even when applied in vast molar excess over ADM [2].

Interestingly, animal and human data reveal a strong, dose-dependent *increase* of plasma ADM concentrations upon adredezumab infusion [3, 4], which cannot be explained by increased production of ADM. A mechanistic explanation for this occurrence was recently proposed [5]. Excess antibody that remains in the circulation is thought to drain ADM from the interstitium into the circulation, since ADM is small enough to cross the endothelial barrier, whereas the antibody is not. While adredezumab only partially inhibits ADM signaling, the strong concentration increase of ADM (complexed with

adredezumab) in the circulation is thought to result in an overall “net” increase of ADM activity on endothelial cells, augmenting endothelial barrier stabilizing effects, while decreased concentrations of ADM in the interstitium reduce vasodilatory effects on vascular smooth muscle cells. The combination of attenuation of both endothelial leakage and vasodilation likely represents the therapeutic potential of adredezumab. This hypothesis fits well with previous studies that showed beneficial effects of ADM agonists in animal models of shock, while complete inhibition of ADM did not improve outcome.

As is mentioned by the authors, a proof-of-concept and dose-finding phase II study with adredezumab is currently ongoing in patients with septic shock and elevated levels of ADM (ClinicalTrials.gov identifier NCT03085758). This trial incorporates a number of innovative features such as a novel composite efficacy endpoint and biomarker-guided patient selection (enrolment based on bio-ADM level), making it one of the first personalized treatment trials in sepsis.

#### Abbreviation

ADM: Adrenomedullin

#### Authors' contributions

CG drafted the manuscript. PP critically reviewed the manuscript. Both approve the final manuscript.

#### Competing interests

C. Geven received travel reimbursements from Adrenomed AG (the company that developed Adredezumab). P. Pickkers received travel reimbursements and consultancy fees from Adrenomed AG. P. Pickkers's institution received a research grant from Adrenomed AG.

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\* Correspondence: [peter.pickkers@radboudumc.nl](mailto:peter.pickkers@radboudumc.nl)

<sup>1</sup>Department of Intensive Care Medicine, Radboud University Medical Center, PO Box 9101, Internal Mail 710, Nijmegen 6500 HB, The Netherlands

<sup>2</sup>Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands



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