Significance of adrenomedullin and the role of adrecizumab in sepsis

To the Editor,

In sepsis, there is damage to vascular integrity i.e., the vascular endothelium as a result of which there is vasodilation, edema, hypotension, and organ failure, which leads to significant morbidity and mortality. Once vascular endothelium is breached, there is a distributive shock, which eventually requires vasoconstrictors if not addressed on time and managed appropriately.

Adrenomedullin (ADM) is a free-circulating peptide hormone, which is responsible for the regulation of vascular tone and stabilization of the endothelial barrier. Adrenomedullin (ADM) is a free-circulating, 52-amino acid peptide hormone belonging to the calcitonin gene–related peptide family. ADM helps in the regulation of vascular integrity and vasodilatation. Studies have shown that in patients with septic shock there is increased levels of bioactive ADM, which has served as a prognostic marker in defining the severity of shock and also mortality. ADM is produced by endothelial cells, vascular smooth muscle cells (VSMCs), monocytes, renal parenchymal cells, and macrophages. Situations such as inflammation, hypoxia, oxidative stress, and surgery are commonly encountered in clinical situations when ADM levels are elevated in the blood. In experimental studies, ADM administration has been shown to be effective in certain models of endotoxemia and lung, liver, and kidney injury. ADM has a short half-life (22 min); therefore, it has to be administered as a continuous infusion till clinically important endpoints are achieved based on clinician’s discretion. One important concern is deleterious effects on hemodynamics with ADM infusion, which is undesirable. ADM has been referred to as a double-edged sword because in health it maintains vascular tone but when administered intravenously in septic patients, it leads to vasodilatation and a compensatory increase in heart rate, which is detrimental. Unfavorable issues are seen when ADM is used in higher doses. Thereafter, clinicians investigated molecules that could modulate or antagonize ADM, which led to the development of adrecizumab (ADZ).

ADZ or HAM 8101 (name during experimental phase) is a humanized targeted therapy directed against the N-terminus of ADM. ADZ is a non-neutralizing, anti-ADM antibody that binds to excessive ADM in sepsis. It is produced for clinical use using Chinese hamster ovary cells. ADZ inhibits increased circulating levels of ADM due to sepsis, protects the endothelial barrier, and decreases interstitial vasodilatory effects mediated via ADM. It binds to the circulating ADM released due to sepsis, stimulates ADM’s beneficial effects such as maintaining the endothelial barrier, preventing
Letters to Editor

Submitted: 19-Dec-2020, Revised: 20-Dec-2020, Accepted: 20-Dec-2020, Published: 01-Apr-2021

References

1. Caironi P, Latini R, Struck J, Hartmann O, Bergmann A, Maggio G, et al. Circulating biologically active adrenomedullin (bio-ADM) predicts hemodynamic support requirement and mortality during sepsis. Chest 2017;152:312-20.

2. Kim H, Hur M, Struck J, Bergmann A, Di Somma S. Circulating biologically active adrenomedullin predicts organ failure and mortality in sepsis. Ann Lab Med 2019;39:454-63.

3. Temmesfeld-Wollbrück B, Brell B, Dávid I, Dorenberg M, Adolfs J, Schmeck B, et al. Adrenomedullin reduces vascular hyperpermeability and improves survival in rat septic shock. Intensive Care Med 2007;33:703-10.

4. Li Q, Wang BS, Yang L, Peng C, Ma LB, Chai C. Assessment of adrenomedullin and proadrenomedullin as predictors of mortality in septic patients: A systematic review and meta-analysis. Med Intensiva 2019;20:212-3.

5. Deniu B, Takagi K, Asakage A, Mebazaa A. Adrecizumab: An investigational agent for the biomarker-guided treatment of sepsis. Expert Opin Investig Drugs 2020. doi: 10.1080/13543784.2021.1857365. Online ahead of print.

6. Geven C, van Lier D, Blet A, Peelen R, Ten Elzen B, Mebazaa A, et al. Safety, tolerability and pharmacokinetics/pharmacodynamics of the adrenomedullin antibody adrecizumab in a first-in-human study and during experimental human endotoxaemia in healthy subjects. Br J Clin Pharmacol 2018;84:2129-41.

7. Geven C, Blet A, Kox M, Hartmann O, Struck J, Bergmann A, et al. Circulating biologically active adrenomedullin (bio-ADM) predicts hemodynamic support requirement and mortality during sepsis. Chest 2017;152:312-20.

8. Temmesfeld-Wollbrück B, Brell B, Dávid I, Dorenberg M, Adolfs J, Schmeck B, et al. Adrenomedullin reduces vascular hyperpermeability and improves survival in rat septic shock. Intensive Care Med 2007;33:703-10.

9. Geven C, van Lier D, Blet A, Peelen R, Ten Elzen B, Mebazaa A, et al. Safety, tolerability and pharmacokinetics/pharmacodynamics of the adrenomedullin antibody adrecizumab in a first-in-human study and during experimental human endotoxaemia in healthy subjects. Br J Clin Pharmacol 2018;84:2129-41.

10. Geven C, Blet A, Kox M, Hartmann O, Seiglma P, Zimmermann J, et al. A double-blind, placebo-controlled, randomised, multicentre, proof-of-concept and dose-finding phase II clinical trial to investigate the safety, tolerability and efficacy of adrecizumab in patients with septic shock and elevated adrenomedullin concentration (AdrenOSS-2). BMJ Open 2019;9:e024475.

Abhijit Nair

Department of Anaesthesiology, Ibra Hospital, Ministry of Health-Oman, P.O. Box 275, Ibra-414, Sultanate of Oman

Address for correspondence:
Dr. Abhijit Nair,
Department of Anaesthesiology, Ibra Hospital, Ministry of Health-Oman, P.O. Box 275, Ibra-414, Sultanate of Oman.
E-mail: abhijitnair95@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Access this article online

Website:
www.saudija.org

DOI:
10.4103/sja.sja_1198_20

How to cite this article: Nair A. Significance of adrenomedullin and role of adrecizumab in sepsis. Saudi J Anaesth 2021;15:228-9.

© 2021 Saudi Journal of Anesthesia | Published by Wolters Kluwer - Medknow