

**Subject:**

Nephrology Rotation

**Homework:**

Erythropoietin stimulating agents resistance & mechanism of ACE inhibitors and ARBs in resiatance

**Instructor:**

Dr. Sona Ladadweh

**Name:**

Noor Ayman Kamel Aburub

**ID:** 1151170

**Erythropoietin-stimulating agents resistance -according to Medscape-:** It is the need for > 150 units/kg of ESA at least 3 times per week or the sudden response refractoriness to a previous stable maintenance dose, such as falling of hemoglobin levels below the target.

**Causes of ESA’s resistance:**

1. Iron deficiency: the most common cause, so its important to check iron stores before starting ESA therapy.
2. Chronic infection/inflammatory state: mainly due to inflammatory cytokines (eg, IL-1).
3. Hyperparathyroidism.
4. Severe malnutrition.
5. Cancer and chemotherapy.
6. Bleeding.
7. ACE inhibitors and ARBs.

**Mechanism of ESA’s resistance by ACE inhibitors and ARBs:**

There is no clear mechanism of resistance by ACEI and ARBs, however there are many postulated hypotheses that may be responsible to ESA’s resistance.

1. Renin-angiotensin system (RAAS) is linked with the synthesis of endogenous erythropoietin in peritubular fibroblasts of the kidney, so when RAAS is activated, erythropoietin production will be enhanced. Thus, using ACEI or ARBs will inhibit RAAS and suppress erythropoiesis process. However, this reduction in erythropoietin can be corrected easily with giving exogenous erythropoietin. Yet, hemoglobin levels can fall more significantly in patients with ACEI and ARBs, which means that there are other mechanisms by ACEI and ARBs.
2. In *vitro*, angiotensin II can activate erythroid progenitor cell growth, when we give ACEI or ARBs the action of angiotensin II is inhibited.
3. N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) is a natural stem cell regulator that inhibits the recruitment of haemopoietic stem cells and normal early progenitors into the S-phase. It was found that ACE inhibitors increase the concentration of this regulator and so inhibits erythroid growth.
4. It has been shown that ACEI reduce the production of interleukin-12 (IL-12) which is a cytokine also enhances erythropoiesis.

Finally, ACE gene polymorphisms influence ACE serum activity. Thus, some patients may be more susceptible to ESA resistance when using ACE and ARB inhibitors. The exclusion of these therapeutic classes for the treatment of hypertension in these patients can be an interesting strategy to optimize the treatment of anemia.

**References:**

1. How is ESA resistance defined in patients with anemia of chronic disease and renal failure, and what are the common causes of resistance? (2020, May 20). Retrieved November 14, 2020, from <https://www.medscape.com/answers/1389854-91825/how-is-esa-resistance-defined-in-patients-with-anemia-of-chronic-disease-and-renal-failure-and-what-are-the-common-causes-of-resistance>
2. Macdougall, I. (1999, August 01). Role of ACE inhibitors and angiotensin II receptor blockers in the response to epoetin. Retrieved November 14, 2020, from <https://academic.oup.com/ndt/article/14/8/1836/1808507>
3. Santos, E., Dias, R., Lima, J., Filho, N., &amp; Santos, A. (2020, October 08). [Full text] Erythropoietin Resistance in Patients with Chronic Kidney Disease: Cur: IJNRD. Retrieved November 14, 2020, from <https://www.dovepress.com/erythropoietin-resistance-in-patients-with-chronic-kidney-disease-curr-peer-reviewed-fulltext-article-IJNRD>