

ESA Hyporesponsiveness

In Chronic kidney disease, anemia is considered as an independent risk factor for cardiac disease and mortality. With the introduction of erythropoietin for almost two decades now, significant reduction in related morbidity, cardiovascular mortality and improvement in cognitive function, exercise tolerance and overall quality of life is seen. About 5-10% of chronic kidney disease (CKD) patients exhibit inadequate response to erythropoietin stimulating agents (ESA)¹. ESA hypo-responsiveness is defined as no increase in hemoglobin (Hb) concentration from baseline after the first month with appropriate weight-based dosing while acquired ESA hypo-responsiveness during treatment is defined if requiring increase in ESA doses up to 50% beyond the dose at which they were maintaining a stable Hb concentration². Another definition for ESA hyporesponsiveness is the need for greater than 300 IU/kg per week EPO or 1.5 mg/kg per week darbopoeitin administered by the subcutaneous route or 400 or 450 IU/kg EPO per week by intravenous route. Dose dependent response to erythropoietin was shown earlier and almost 90 % CKD patient respond to high doses. Various other factors contribute to erythropoietin resistance and poor quality of life³.

Erythropoietin hypo-responsiveness was explained primarily due to inflammatory state of CKD, that is having increased levels of inflammatory markers such as C-reactive protein, cytokines IL-1, IL-6, interferon (IFN)- α and tumor necrosis factor (TNF)⁴. Inflammatory markers induce EPO resistance indirectly by up regulation of hepcidin which is a type II acute phase protein produced in the liver and inhibit iron metabolism. The cytokines also inhibit the growth of erythroid precursor cells and impair activation of the EPO receptor. Spontaneous absence of dimerization of the EPO receptor and their decreased number due to receptor internalization and degradation due to unexplained mechanism in addition results in impaired response to ESA.

Multiple studies have proved the inflammatory state of CKD as direct factor for refractoriness or resistance response to erythropoietin and therefore adequate dialysis is advised prior to change in ESA dosage⁵. In India and other developing countries where cost remains the main hindrance for maintaining treatment adequacy, one has to ensure regular dialysis and compliance to ESA dosage prior to escalating EPO dosage and declaring hypo-responsiveness.⁶ The other indirect correctable factors that need evaluation are to assess for other causes of anemia such as iron deficiency, vitamin B12 and folate deficiency, serum parathyroid hormone and drugs ACEi/ARB usage. Correction of above factors along with regular monitoring for secondary hyperparathyroidism and subclinical aluminum toxicity improve dose response to ESA⁷. Usage of adjuvant to ESA treatment such as androgens, vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline has been described. Studies have shown the role of adjuvant treatment in EPO hypo-responsiveness but still enough data is lacking for their recommendations. Two single center studies by Nityanand et al have published in this issue described the role of pentoxifylline and vitamin E here and their association with inflammatory markers. Though the studies were limited by small number of subjects and duration but are well designed and analyzed. They have shown relation of inflammatory markers CRP, ESR, TNF- α with the persisting low Hb on erythropoietin and role of pentoxifylline and vitamin E. Pentoxifylline is a non-selective phosphodiesterase inhibitor, inhibits TNF and leukotriene synthesis and reduces inflammation. 20 subjects were included in study on pentoxifylline, who had no improvement on adequate ESA dosage for 2 months. With the addition of drug for 4 months statistical significant rise in Hb was seen. The second study with 25 subjects also showed significant improvement in ESA hypo-responsiveness with the addition of vitamin E. Several studies on adjuvant treatment in ESA hypo-responsiveness have been inconclusive, suggesting the need for large studies and good randomized trial to prove the role of adjuvant treatment and their recommendation on the emerging issue of erythropoietin hypo-responsiveness.

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