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Biological basis for rational use of erythropoietin stimulating agents

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Erythropoietin stimulating agents have been instrumental in improving the lives of patients on dialysis, decreasing transfusions, and reducing sensitization. However over the past 10 years, there have been a number of large clinical trials such as TREAT, CHOIR, and the Normal Hematocrit Study demonstrating that targeting a higher hematocrit leads to worse outcomes. In addition, trials have demonstrated that higher doses of erythropoietin lead to a higher recurrence of cancers. What has been lacking is a biologic basis for these untoward results. There are two known receptors for erythropoietin, the homodimeric erythropoietin receptor, responsible for erythropoiesis, and the more ubiquitous heterodimeric erythropoietin receptor consisting of an erythropoietin receptor and the beta-common receptor. These receptors have different Km's with the Km of the heterodimeric erythropoietin receptor/beta-common receptor being ten-fold higher than the homodimeric erythropoietin receptor. Thus, targeting a higher hemoglobin with larger doses of erythropoietin stimulating agent increases the likelihood of stimulation of the heterodimeric erythropoietin receptor/beta-common receptor. Our work has demonstrated that stimulating the heterodimeric erythropoietin receptor/beta-common receptor can explain all of the untoward events seen in the clinical trials. Thus understand the biology of both erythropoietin receptors leads to a rational set of guidelines for use of erythropoietin stimulating agents and a rational set of guidelines to predict the safety profile of the novel agents to stimulate erythropoiesis.

Biography

Mark S Segal did his undergraduate work at MIT and was than recruited to the MD/PhD program at The University of Texas Southwestern Medical Center at Dallas. He did his internship and residency at The University of Texas Southwestern Medical Center at Dallas, and did his Nephrology fellowship training at Beth Israel Deaconess Medical Center. He was then recruited to University of Florida in 1999 and was appointed Chief of the Division of Nephrology in 2010. He is well funded for his research on markers of vascular health and has presented his research at national and international meetings.

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