Rebuttal: PRO Position

Should Hemoglobin Targets for Anemic Patients with Chronic Kidney Disease Be Changed?

Ajay K. Singh

Renal Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass., USA

Dr. Locatelli feels my cautious approach of treating anemia with conservative doses of ESA might return us to a pre-ESA era. On the contrary, I hope not and believe that it would bring the USA more in line with practices elsewhere in the world. In the US, cumulative ESA doses are much higher than in Europe and Japan. For example, Greenwood et al. [1] report the mean erythropoietin dose in the United States at 19,569 and 7,992 IU/week in the United Kingdom Renal Registry facilities. Similar data is available from the Dialysis Outcomes and Practice Patterns Study (DOPPS) [2]. Furthermore, USRDS data shows that >50% of dialysis patients have Hb concentrations >12 g/dl. Introducing an Hb threshold of >9 g/dl would help this US problem. Being conservative makes the US look more like Europe and elsewhere – what would be wrong with that?

Dr. Locatelli discusses the TREAT study in some detail. He argues that since subjects assigned to the placebo rescue arm achieved an Hb 'very close' to the levels recommended in the guidelines, the Hb guidelines should not be changed. On the contrary, because the placebo rescue arm in TREAT achieved Hb levels similar to the FDA recommended range without exposure to a significant dose of ESA (median and mean darbepoetin doses of 0 µg and 5 µg/month, respectively), the guidelines should be changed to recommend, 'In most nondialysis CKD patients, anemia can be treated without the use of ESAs'. In dialysis CKD, more flexibility is required and ESA-sparing strategies should be pursued [3].

Second, Dr. Locatelli argues that stroke was not a primary end point in TREAT, and because the trial was not powered for reduction in the rate of stroke, the highly significant p value associated with the increased hazard of a stroke with darbepoetin treatment should be ignored. Stroke was a pre-specified cardiovascular outcome. While the absolute risk of stroke was low, applied to the whole CKD population, the stroke safety signal is meaningful. From a purely safety-oriented perspective, the stroke signal in TREAT should be considered in making treatment decisions regarding ESAs in nondialysis CKD patients, and it should also raise concern in dialysis patients where data from the Canada-Europe study indicates that the stroke risk was greater in the high hemoglobin-high epoetin dose group ($p = 0.045$) [4].

Lastly, Dr. Locatelli uses the heterogeneity in clinical signals between CHOIR, CREATE and TREAT to argue that these studies somehow invalidate each other. As I have discussed elsewhere [5], various differences in the four RCTs might provide an explanation. About 50% of the study population in CHOIR were diabetic as were 25% of the patients in CREATE, whereas 100% of patients were diabetic in TREAT. Other differences were the use of different ESA doses and that the trials used different ESAs.

Since hemoglobin is an unreliable surrogate, a two-pronged strategy makes more sense: a minimum Hb threshold of 9 g/dl (because there is evidence to support this) and a shifting in focus to using the lowest possible

ESA dose to achieve the clinical goal individualized for the patient (be it quality of life improvement or blood transfusion avoidance).

Disclosure Statement

Dr. Singh was Principal Investigator of the CHOIR study and a member of the executive committee for the TREAT study. He presented to the FDA Cardiovascular Disease and Renal Advisory Committee (CDRAC) in September 2007 and to the US Congress House of Representatives, Ways and Means Committee, in December 2006 and June 2007. Dr. Singh reports receiving consulting income from Amgen, Johnson and Johnson, Fibrogen, and Watson. He reports receiving grant support from Amgen, Johnson and Johnson and Watson.

References

- 1 Greenwood RN, Ronco C, Gastaldon F, Brendolan A, Homel P, Usvyat L, Bruno L, Carter M, Levin NW: Erythropoietin dose variation in different facilities in different countries and its relationship to drug resistance. *Kidney Int Suppl* 2003;87:S78–S86.
- 2 Pisoni RL, Bragg-Gresham JL, Young EW, Akizawa T, Asano Y, Locatelli F, Bommer J, Cruz JM, Kerr PG, Mendelssohn DC, Held PJ, Port FK: Anemia management and outcomes from 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2004;44:94–111.
- 3 Singh AK: ESAs in dialysis patients: are you a hedgehog or a fox? *J Am Soc Nephrol* 2010;21:543–546.
- 4 Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D: Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol* 2005;16:2180–2189.
- 5 Singh AK: Does TREAT give the boot to ESAs in the treatment of CKD anemia? *J Am Soc Nephrol* 2010;21:2–6.