

Key insights into present and future treatments of anaemia in CKD patients

Angel L. M. de Francisco

Servicio de Nefrología, Hospital Universitario Valdecilla, Santander, Spain

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Introduction

The introduction of erythropoiesis-stimulating agents (ESAs) revolutionized the management of anaemia in chronic kidney disease (CKD) patients by providing effective control of haemoglobin (Hb) levels, reducing the need for blood transfusions and improving patient quality of life. The use of ESAs in CKD patients is constantly evolving as new research helps us to better understand how to safely and effectively manage anaemia in these patients. This supplement reviews the latest thinking on optimal Hb control and looks to the future in the increasingly complex landscape of ESA therapies.

Anaemia has been recognized as a risk factor for the development of cardiovascular disease (CVD) in CKD patients and CVD remains the leading cause of hospitalization and death in these patients. In their chapter entitled 'Future perspectives on treatment with erythropoiesis stimulating agents' in high-risk patients, Stefan Anker and Robert Toto review several large-scale clinical studies designed to address the question of whether effective management of anaemia can improve cardiovascular (CV) outcomes. Results of the CHOIR [1] and CREATE [2] studies are discussed, along with two more recent studies, TREAT (Trial to Reduce cardiovascular Events with Aranesp Therapy) [3,4] and the RED-HF (Reduction of Events with Darbepoetin alfa in Heart Failure) trial [5], which are currently ongoing. The latter randomized controlled studies are anticipated to shed light on ESA safety at higher target Hb levels and it is hoped that they will provide the conclusive data still needed to establish the impact of anaemia therapy on CVD in these patients.

In their chapter entitled 'Use of darbepoetin alfa in the treatment of anaemia of chronic kidney disease: clinical and pharmacoeconomic considerations', Fernando Carrera and Michel Burnier provide an overview of the use of the ESA, darbepoetin alfa (Aranesp[®]), in the treatment of anaemia in CKD patients. Darbepoetin alfa, the first longer-acting ESA, has been shown to offer a number of further clinical and economic benefits over the shorter-acting epoetins, epoetin alfa and beta. Several studies are discussed, which demonstrate that patients either not on dialysis or receiving dialysis can be successfully switched from epoetin to darbepoetin alfa at extended dosing intervals, with no compromise in efficacy and with significant dose savings. In addition to the convenience afforded by extended dosing intervals, pharmacoeconomic implications are also considered. The MERCURIUS study is expected to provide further information on how improvements could be made in all stages of ESA delivery and utilization in hospitals throughout Europe. Interim data from one centre demonstrate significant cost savings in labour and materials following a switch from epoetin to darbepoetin alfa therapy.

Hb levels that are either too high or too low can have an adverse effect on patient outcomes. Evidence from CHOIR [1] and the Normal Haematocrit Trial [6] has shown that targeting higher versus lower Hb levels (13.5 versus 11.3 g/dL and 14 versus 10 g/dL, respectively) results in an increase in the risk of death and serious CV events in CKD patients. In light of this, and other emerging evidence, treatment targets have recently been re-assessed by regulatory agencies. In the latest revision (March 2008) of the European product labelling (SmPC) for the ESA class of drugs, the target treatment range was lowered to 10–12 g/dL, with a warning not to exceed 12 g/dL [7–13]. It is clear that optimal control of Hb levels is both desirable and essential, yet maintaining patients at Hb levels that are both safe and provide maximal benefit is a continuing challenge. Hb levels in CKD patients have been shown to move up and down during treatment, sometimes with quite extreme fluctuations above and/or below target Hb ranges; it is important, therefore, to understand the causes of Hb fluctuation or variability in order to optimize treatment. Inflammation is believed to play a key role in Hb variability and responsiveness to ESAs in CKD patients. Our third paper, entitled 'Inflammation

Correspondence and offprint requests to: Angel L. M. de Francisco, Presidente de la Sociedad Española de Nefrología, Servicio de Nefrología, Hospital Universitario Valdecilla, Santander, Spain. Tel: +34-942-202738; Fax: +34-942-320415; E-mail: martinal@unican.es

and its impact on anaemia in chronic kidney disease: from haemoglobin variability to hyporesponsiveness', by Angel L. M. de Francisco, Peter Stenvinkel and Sophie Vaumont addresses the complex role of inflammation in CKD, as evidenced by the apparent state of deranged inflammatory markers.

It has been suggested that increased levels of pro-inflammatory cytokines in CKD suppress bone marrow erythropoiesis, reduce erythropoietin production and modulate iron metabolism leading to hyporesponsiveness to ESAs and poor treatment outcomes [14,15]. The mechanisms by which inflammatory cytokines may affect the response to ESAs are examined. In addition, the authors discuss a number of possible strategies or interventions with which to minimize inflammation in these patients and enhance response to ESAs.

In addition to the increasing complexity of maintaining patient Hb levels within narrower margins, the number of available treatment options is also rising, not only with respect to new ESAs, but also with the recent market entry of epoetin biosimilars. Biosimilar molecules are defined as 'biological products referring, but not identical, to existing products, submitted for separate market approval following patent expiration.' In the final paper of the supplement, entitled 'Biosimilar therapeutics-what do we need to consider?', Dr Huub Schellekens highlights some important issues surrounding biosimilars, including variability and inconsistency in structure and purity, the impact of this variability on patient safety and the need for further regulations (to supplement those currently in place) for their approval and use.

In summary, this supplement provides an informative discussion of the important issues of the day surrounding the use of ESAs in patients with CKD. Ongoing research, discussed herein, will continue to enlighten this complicated area, ultimately leading to safer more effective use of these agents.

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