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REVIEW

Anaemia in chronic kidney disease – a review

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The management of anaemia in chronic kidney disease (CKD) patients is a complex, multifaceted process reliant on the administration of exogenous erythropoiesis stimulating agents (ESAs) and iron supplements to ensure the adequate production of viable erythrocytes. Recommended best practice guidelines should be adhered to in order to ensure favourable treatment outcomes whilst minimising the risks often associated with ESA therapy. A paucity in readily available, accurate data makes quantifying the extent to which renal anaemia affects our population and how it is managed challenging, however it is expected to follow international trends. Novel preparations for treating renal anaemia are currently in the clinical trial phase, therefore the potential benefits and risks have yet to be confirmed.

Prevalence estimates in South Africa

Renal anaemia is the most common comorbid condition associated with chronic kidney disease (CKD) and ultimately develops in nearly all CKD patients during the disease's natural progression.[1] Estimates have indicated that at least 90% of patients undergoing haemodialysis (HD) are anaemic.[2] In 2016 the Global Burden of Disease (GBD) study ranked CKD as the 16th leading cause of mortality and predicted that it would rank as the 5th leading cause of mortality by the year 2040.[3] The National Kidney Foundation of South Africa (NKFSA) estimated that South Africa had five million adult CKD patients in the year 2015, i.e. approximately 10% of the population at the time.[4] The paucity of accurate data in conjunction with the age of data currently available to us makes accurate estimates of the number of patients affected by renal anaemia challenging.[5] The South African Renal Registry (SARR) was established in an attempt to bridge the data gap, however its scope of data collection is limited to patients undergoing renal replacement therapy (RRT) for end stage renal disease (ESRD) and their last report, dated 2017, was published in 2019.[6] The paucity of data is compounded by patients residing in a rural setting with limited access to treatment facilities and is further compounded by the fact that the majority of renal failure/renal anaemia cases are typically asymptomatic until ESRD manifests.[4]

Physiological response to a hypoxic state

The physiological compensation to the resultant hypoxic state attributed to anaemia results in the upregulation of hypoxia-inducible factors (HIFs) triggering a sequence of upregulation events aimed at correcting the hypoxic state at a systemic and cellular level.[7] The decrease in circulating erythrocytes implies the decreased ability for oxygen demands to be met which, in turn, stimulates the kidneys to produce erythropoietin (EPO). Erythroid progenitors in the bone marrow are stimulated by EPO to increase the production of haematopoietic stem cells and the final outcome of the process is the release of matured erythrocytes into circulation approximately seven to ten days later.[8] Renal failure due to CKD thus impedes the process as the kidney not only loses its excretory function, its endocrine function wanes and EPO production diminishes.

Treating renal anaemia

The treatment of renal anaemia is reliant on the administration of exogenous erythropoiesis stimulating agents (ESAs) and the co-administration of iron supplements to maintain the body's ability to produce viable erythrocytes.[9,10] The advent of biotechnology has simplified the production of recombinant human erythropoietin (rhEPO) through culturing in mammalian cell lines and various EPO preparations exist which are categorised according to their glycosylation patterns, i.e. α, β, θ and ζ.[7] Novel preparations also exist which differ to an even greater extent from endogenous EPO, such as darbepoetin-α (Aranesp®) and methoxy polyethylene glycol-erythropoietin-β (Mircera®), offering a longer half-life.[11] Differences in pharmacokinetics aside, a meta-analysis on the various preparations of EPO has proven that no ESA can claim superiority over another on the basis of safety or efficacy.[12] Decades ago the use of ESA therapy to achieve and maintain serum haemoglobin (Hb) levels > 13 g/dl was advocated, citing decreased risks for adverse cardiovascular events and the potential to retard CKD disease progression.[13] Over the course of time the Correction of Haemoglobin and Outcomes in Renal Insufficiency (CHOIR) and Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) studies have proven that Hb levels closer to 11.5 g/dl significantly lower the risks of adverse cardiovascular events.[14,15] Current treatment guidelines by the South African Renal Society (SARS) recommend the initiation of ESA therapy when Hb levels diminish to < 10 g/dl and for maintaining Hb levels < 10 g/dl < 12.[16] Upon stabilising haemodynamic parameters for a patient it is recommended that a full blood count and iron status assessment be conducted at least quarterly.[16] Parenteral iron supplementation is easily administered during HD sessions and ferrous gluconate is a suitable preparation. In a similar manner to that of the various ESA preparations, iron preparations differ in the ability to be reduced to elemental iron, with the ferrous

oxidation state of iron being the physiologically active form that is readily incorporated into Hb.[17]

International trends on erythropoiesis stimulating agent therapy use

Data gathered through the Dialysis Outcomes and Practice Patterns Study (DOPPS) found that the prescription of higher doses of ESA treatment and the resultant overshoot of the recommended upper Hb target is a globally present phenomenon.[18,19] It is therefore expected that South African data may show similar trends.

Future prospects for treating anaemia

A new class of therapeutic agents known as HIF prolyl hydroxylase inhibitors or HIF stabilisers serve to maintain the upregulation of erythropoiesis by preventing HIF degradation and are thought to be effective in the treatment of renal anaemia, even for patients with ESRD.[20] These agents are administered orally and may prove to be a more favourable option to patients, especially when not yet dependent on dialysis.[21] Currently there are several candidate compounds undergoing phase three clinical trials and it is hypothesised that the induction of more consistent erythropoiesis without the exogenous administration of ESAs may be associated with a decreased risk for adverse cardiovascular effects, albeit limited to comparable Hb levels.[21] Despite the preliminarily positive outcomes noted, concerns still exist over the long-term safety of maintaining elevated HIF levels, especially for its effects on tumorigenesis and angiogenesis driven by upregulated vascular endothelial growth factor (VEGF) levels.[22]

Conclusion

It is evident that best practice guidelines should be adhered to in order to secure the best possible patient outcome whilst reigning in the risk of adverse events associated with anaemia itself and furthermore the risks of adverse events associated with ESA therapy. The HIF prolyl hydroxylase inhibitors have thus far proven non-inferior to the ESA treatment options currently to our avail, however, should marketing authorisations be granted for the novel therapeutic agents, identifying patients who are unlikely to benefit from these will be essential to obtaining the most favourable treatment outcomes.

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