Virtual discussion on anaemia in chronic kidney disease

A group of renal experts attended a round-table meeting to discuss anaemia in chronic kidney disease. Here, Jasmine Callaghan, *Journal of Kidney Care* (*JKC*) Editor, details the outcomes

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On 12 October 2020, the *Journal of Kidney Care* (*JKC*) and Astellas held a virtual discussion on anaemia in chronic kidney disease (CKD).

The panel included five consultant nephrologists (of which, three are professors of renal medicine or nephrology), one anaemia matron, one lead anaemia nurse and a renal pharmacist, who are based in Scotland, Wales and across England.

The objectives of this meeting were to:

- Identify reasons for sub-optimal identification/underdiagnosis of anaemia in patients with CKD
- Discuss challenges associated with current classes of treatments for anaemia in CKD and determine whether the current standard of care is able to address them
- Provide clinicians from the multidisciplinary team (consultants/nurses/pharmacists) with a forum to discuss regional variations and local challenges.

Prevalence and incidence of anaemia in chronic kidney disease

To begin, the panel discussed their clinical experiences with CKD, pre-dialysis, dialysis and transplant populations within their various renal settings.

The panel reported that, in the pre-dialysis population, the management of anaemia takes up a significant amount of their renal care time. One panel member reported that 90% of peritoneal dialysis (PD) patients were receiving treatment for anaemia, of whom 28% had haemoglobin levels less than 100 g/l, while 75% of nephrology outpatients and low-clearance patients were receiving treatment for anaemia, of whom 17% had haemoglobin levels less than 100 g/l. Thus, the majority of CKD stage 4 and 5 patients had anaemia and were receiving treatment for it.

Another panellist stated that 95% of the haemodialysis (HD) population in their hospital were receiving some form of anaemia therapy. In the PD population at the same hospital, a slightly lower number of patients were being treated with erythropoiesis-stimulating agents (ESA), as most received iron intermittently.

Regarding the CKD population, approximately 30–35% were receiving treatment for anaemia; however, although a good percentage of this group receive treatment for anaemia, there is a need for further strategies to streamline the anaemia care provided.

Panellists noted that the way in which anaemia is treated has changed significantly over the past 10 years. In the past, nephrologists proactively prescribed ESA to treat anaemia in CKD patients, whereas there is now a tendency to adopt a more cautious approach in prescribing this therapy in general. A large percentage of HD patients are treated with intravenous (IV) iron and ESA, although this figure is lower in PD patients.

To conclude, one panel member detailed how, in 2015 at their London hospital, 675 patients were on ESA, compared to 1121 in 2020. However, not all areas in the UK have reported such an increase in the number of ESA-treated patients, which could be partly due to more judicious use of ESA according to current guidelines, and more proactive IV iron therapy. The panellists agreed that diagnoses and treatment were improving and increasing. All the incidence statistics were similar across the panel, with only a small number of transplant patients on ESA.

Diagnosing anaemia in chronic kidney disease

The chair then moved the panel's discussion onto how patients are referred to low clearance clinics. The criteria determining how patients are referred to low clearance differed from hospital to hospital, indicating that standardisation across settings may be helpful. Once a patient is referred to a low clearance clinic, their needs can be addressed. The testing process therefore needs to be improved to ensure that these patients are identified.

One participant detailed how the criteria for entering a low clearance clinic was becoming increasingly more complicated, and includes the use of kidney failure risk equations, age, eGFR, and essentially whether nephrologists had evidence that a patient will need pre-dialysis care.

The discussion soon progressed onto the tests that are used to diagnose anaemia, whether they are appropriate and whether anyone on the panel used other methods in conjunction with them. One participant began with a focus on the dialysis population, detailing how the National Institute for Health and Care Excellence (NICE) guidance (2015) was implemented when using reticulocyte haemoglobin equivalents (RET-He). Their diagnostic tests consist of monthly RET-Hes and transferrin saturations (TSATs) and periodic (3-monthly) ferritins.

Furthermore, HD and PD patients are tested with RET-He and TSATs. When CKD patients are referred, renal professionals are more reliant on TSATs and ferritin, but once they are in the system, further diagnostic tests can be used.

While the panel adhered to the NICE guidelines (2015) in most cases, they identified that the uptake and implementation of the tests recommended to determine iron status were problematic. The guidelines suggest that either percentage hypochromic red blood cells (%HRC) or reticulocyte haemoglobin content (CHr) should be used firstline or, where this is not possible, a combination of serum ferritin and TSAT.

A panel member detailed how the clinical use of %HRC is limited by sample stability and the need for processing within 6 hours of phelobotomy for the test to be reliable. %HRC and, to a lesser extent, CHr are limited by test analyser availability and by the clinical utility of an equivalent test; while Ret-He is recommended as an equivalent test to CHr, HYPO-He as a possible alternative to %HRC has a poorly defined diagnostic threshold and limited clinical evidence.

A panel member who had experience in the use of Ret-he and HYPO-He in HD patients suggested that the incidence of iron deficiency in this population differed significantly depending on the test used (Ret-He versus TSAT or ferritin, or the combination of TSAT and ferritin). Ret-He seemed to offer an alternative insight into possible iron-restricted erythropoiesis. However, for these reasons, many renal units continue to use the traditional markers of TSAT and ferritin.

Participants agreed that using different testing measures can identify more patients for treatment, so it does depend on how different renal settings use them. Due to the limitations, and lack of availability of some of the tests recommended by NICE to evaluate iron status in dialysis patients, participants agreed that some centres may find it difficult to implement and fully comply with the NICE guidelines (NICE, 2015).

Patient quality of life and guiding anaemia diagnosis and management

Next, the panel discussed how much patient-reported quality of life impacted how anaemia is assessed and managed.

The topic of patient-reported experiences (PREMs) and patient-reported outcomes (PROMs) soon arose. One centre, acknowledging that PROMs and PREMs relating to anaemia are limited, reported their own experience, where a standardised patient questionnaire has been recently introduced for CKD patients receiving IV iron to provide an insight into their feelings about treatment, and may help guide future practice. This questionnaire is used pre- and post-treatment with IV iron.

The rest of the panel detailed how, in clinical practice, as opposed to clinical trials, and other than a follow-up system in one case, a well-structured way of measuring and capturing PREMs and PROMs was not in place. However, they thought that implementation of this would be valuable in their hospital settings.

Interestingly, one participant asked the panel member whose centre was conducting the survey what they considered to be more important in deciding to treat a patient: the patient's reported symptoms, or their serum ferritin or haemoglobin levels, as the benefits of treatment cannot always be quantified. The reply was that the two approaches are not mutually exclusive and that understanding the patient's reported response to treatment could help facilitate an individualised approach to treatment. By starting to collect patient-reported outcomes and experiences, renal professionals may be able to understand how various treatments address outcomes that are important to patients and then use this information to guide future decision-making. As this is done on an individualised, case-by-case basis, it cannot be generalised to the entire patient population.

It was also noted that a problem with recording patient outcomes is that, in the majority of cases, it is very difficult to get enough patients to fill out the forms to generate sufficient data, and that some patients developed questionnaire fatigue. All the panellists observed patient questionnaire fatigue, and experienced difficulty in quantifying the crucial element of quality of life that could inform clinical decision-making or justify continuing or changing the patient's treatment journey.

Some panel members suggested that PROMs could be subject to bias. The panellists all agreed that there was often a discrepancy between the test results and the patient's reported symptoms, so it is important to consider both and endeavour to make an informed clinical decision of how best to proceed with the patient's treatment.

The panel commented that there are countless other ways of measuring patient activity, including apps and Fitbits. If patients are open to sharing their data, these methods could offer a valuable insight into their quality of life, thus avoiding or reducing the possibility of questionnaire fatigue.

Lastly, several members of the panel noted the discrepancies between what patients told their doctors about their quality of life and either what they told their nurses or what the patient's partner would tell the doctor. Often, during a consultation, the patient would detail in positive terms their quality of life to their doctor, while their partner would 'shake their head' while sitting behind them. At other times, nurses would need to patiently sit with the patient, asking how the anaemia was affecting their quality of life until they felt comfortable enough to tell the truth, which can be a slow process. The panel's consensus was that patients may volunteer more information to nurses after their initial consultation with the doctor.

Suitability of approved drugs for anaemia treatment

Many considerations need to be taken into account regarding the treatment of anaemia, not least efficacy, safety and convenience, the latter of which seemed be at the forefront of the discussion.

The frequency of administration of iron therapy has been a recent topic of discussion in renal care, as the panel said that once daily may be as effective as three times daily, as well as more convenient or acceptable to the patient. The way in which an oral treatment is delivered might need to be rethought or an alternative considered. Furthermore, new phosphate binders, which are also a form of iron therapy, may provide an additional tool in the management of iron requirements in CKD patients. The panel then discussed moving the administration of IV iron infusion to pharmacies or GP practices to prevent patients from having to visit hospitals, particularly during the pandemic. One panellist said that they had tried taking IV iron into hospital-like settings, such as the dialysis unit, but essentially, it always has to be given in a place with hospital standard resuscitation facilities.

Another said that, a few years ago, they were asked to consider setting up an iron service within the community, but had been unable to do this due to challenges such as the need for clinical and resuscitation facilities. However, the possibility of setting up an iron service at a GP practice was suggested, as this would allow patients to receive this treatment without having to visit hospital. A key current treatment issue is that the majority of patients require IV iron, but both travel restrictions and COVID-19 risks made it more problematic to visit hospital.

Regarding both short- and long-acting ESA therapy, there is a difference in outcomes and from observational data, and short-acting ESA therapy may be a better option, especially for reducing risk in dialysis patients (Sakaguchi et al, 2019). The panel suggested that some clinicians may find it difficult to switch patients between short- and long-acting ESA therapy. Switching may occur rarely, as often clinicians may have limited understanding or experience regarding the interchangeability and the protocol for conversion.

When asked about epoetin injections, and whether they are now administered by patients at home due to COVID-19, the panel detailed how many patients, particularly the older population, were not prepared to inject themselves, raising the point of whether they should be brought into their local hospital, mindful of the dangers of the pandemic, although this was noted to be a very rare occurrence. However, this has so far been largely avoided during the pandemic as district nurses are now visiting patients who would have normally gone to their GP practice or local hospital to inject treatment or take blood.

The discussion moved onto the future of anaemia treatment. Many noted that treatment should progress in a way that prevents patients from having to make the, at times, lengthy journey to the hospital, where they then have to pay for parking and wait to be seen. Oral iron could be a viable alternative to intravenous infusion.

Furthermore, in terms of oral iron as an alternative to IV iron, one panel member was in favour of trialling the former, unless the patient has severe iron deficiency. Patient safety also needs to be taken into consideration, as well as logistical difficulties and cost; however, most patients do require IV iron at some point and oral iron plays a smaller part in patient pathway considerations. Newer preparations of oral iron, which have not yet been licensed in the UK, have been reported to have better bioavailability (Pergola et al, 2019), which means that they are likely to play a larger role in anaemia treatment in the future.

Another panellist predicted that, in the long term, oral iron preparation will be suitable for patients within the community. However, patients under

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secondary care need an alternative treatment to oral iron preparation. There are several hypoxia-inducible factor prolyl-hydroxylase inhibitors (HIF stabilisers) that are in clinical development (Sanghani and Haase, 2019). HIF stabilisers are predicted to play a role in the treatment of CKD, PD and transplant patients, but not necessarily HD patients, as they are an oral therapy.

From a patient perspective, the biggest complaints regarding treatment were from those who used to receive iron treatment at home and had to make the transition to being treated at their local hospital. Additionally, many patients would welcome treatments with fewer injections, especially as some are needle-phobic, and so might ask why they cannot take oral treatment. Panel members also noted the inconvenience for patients not on dialysis, who were prescribed IV iron, as they have to travel to hospital for the treatment, with the potential for parking fees and long waiting times. However, panellists acknowledged that these visits often coincide with clinical consultations, rather than a journey for IV iron alone.

The panel concluded the discussion on suitability of treatments with a consensus that logistics played a large part in making treatments inconvenient for patients, with one panel member detailing how electronic prescribing and virtual clinics could help address this with high-dose low-frequency iron, long-acting ESA, direct access to a dedicated anaemia team and greater access to blood tests.

Meeting haemoglobin targets set by national guidelines

The panel agreed that their haemoglobin targets were 100–120 g/L. One panel member noted that these targets are sensible for patients treated with ESA, but the upper limit for haemoglobin in CKD patients not on ESA is yet to be defined. Furthermore, targets may continue to move in the future with the introduction of newer therapies, such as HIF stabilisers. However, presently, guidelines may restrict any changes to targets.

The chair then asked whether it would be possible or even easy to conduct a study with target haemoglobin levels of 140 g/L with a new drug that is not an ESA. Panel members thought this could provide a window of opportunity to observe whether this treatment would increase haemoglobin levels and if any adverse cardiovascular events would occur. The nephrologists agreed that they would be comfortable enrolling patients into a study with a target haemoglobin level higher than the standard recommended range. The anaemia nurses commented on the possible difficulties in explaining to patients why they want to raise their haemoglobin levels after long-term advice about keeping them at 100–120 g/L. They noted how they would inform patients that guidelines are being reviewed following research in an attempt to support it.

Redesigning anaemia services in the UK

To conclude, the panel reflected on what changes they would make to improve their services. The answers included developing a reliable self-reporting tool that patients could use to submit haemoglobin levels and symptoms.

Once again, the issue of logistics arose, with panel members suggesting that the availability of services closer to patients would decrease the time spent travelling and waiting to be seen, money spent and carbon footprint. The panel members said that this requires home testing and depends on the treatments available, and whether these still revolved around IV iron, as this needs monitoring.

Home visits, flexibility in delivering treatment, improving the experience of those delivering and receiving treatment, delivery of treatment by GPs and reducing the need for patient contact were all factors identified that could improve the patient journey. With all oral treatments, there is a real opportunity to reduce at least some of these face-to-face visits and redesign anaemia services to meet patients' needs.

Declaration of interest: this article is based on an expert group discussion held in October 2020. Astellas provided financial support to MA Healthcare to facilitate the discussion. The attendees were paid honoraria for their time in panel engagement.

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