Therapeutic options

Pharmacological management of chronic kidney disease and its complications

In the first article in this two-part series, ‘prescribing principles for patients with chronic kidney disease’ (CKD), Christopher Brown outlined the prescribing considerations needed to account for the alterations in drug handling ability in the CKD patient. In this article Christopher focuses on the pharmacological management of common complications of CKD.

Introduction

Many of the kidneys’ endocrine, metabolic and homeostatic functions are lost or compromised in CKD. These manifest in an array of signs and symptoms that can be managed pharmacologically in the early stages. In general, the degree of pharmacological intervention is inversely proportional to the decline in renal function (see Table 1) but early intervention may prevent or reduce the rate of disease progression. Even in established renal failure (ERF) where dialysis replaces some kidney functions pharmacological intervention is necessary to replace the functions that dialysis cannot. Pharmaceutical care is an essential component to the multidisciplinary approach of managing renal disease and much opportunity exists for pharmacists to benefit the health and well-being of CKD patients. Many prescribing decisions rely on sound comprehension and application of the first principles of pharmacokinetics to accommodate either the degree of renal dysfunction or dialysis modality. With the ever increasing ‘renal population’ and the recent expansion in the therapeutic armoury, never before has there been a more prudent time for pharmacists to remain up-to-date with current evidence, practice and guidelines. This article will provide readers with an overview of common complications of CKD and the practice points to consider in the application of national guidelines.

Where to go for guidance?

There are many national and international authorities to direct the best practice and evidence-based management of CKD. The UK Renal Association’s Clinical practice guidelines are for managing kidney disease in the UK and they serve the UK Renal Registry to monitor indicators of the quality of care provided by renal units. The annual publication of the Registry Report allows for benchmarking and comparative audit of quality of care and outcome measures. The current guidelines are the fourth edition and were published in modular form between

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Table 1. Common complications of the different stages of kidney disease*

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>GFR (ml/min/1.73m²)</th>
<th>Description</th>
<th>Likely complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>GFR ≥ 90</td>
<td>Kidney damage but normal GFR</td>
<td>Hypertension more frequent than in people without CKD</td>
</tr>
<tr>
<td>Stage 2</td>
<td>GFR 60–89</td>
<td>Kidney damage with mild impairment</td>
<td>Hypertension frequent</td>
</tr>
<tr>
<td>Stage 3</td>
<td>GFR 30–59</td>
<td>Moderate impairment</td>
<td>Mild elevation of parathyroid hormone</td>
</tr>
<tr>
<td>Stage 3 A**</td>
<td>GFR 45–59</td>
<td></td>
<td>Hypertension common</td>
</tr>
<tr>
<td>Stage 3 B**</td>
<td>GFR 30–44</td>
<td></td>
<td>Decreased calcium absorption</td>
</tr>
<tr>
<td>Stage 4</td>
<td>GFR 15–29</td>
<td>Severe impairment</td>
<td>Reduced phosphate excretion</td>
</tr>
<tr>
<td>Stage 5</td>
<td>GFR &lt;15 or Dialysis</td>
<td>Established renal failure (ERF)</td>
<td>More marked elevation of parathyroid hormone</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Altered lipoprotein metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal anaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>As above but more pronounced plus:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All the above (with greater severity) plus:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- salt and water retention causing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>apparent heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- anorexia and vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- pruritus (itching without skin disease)</td>
</tr>
</tbody>
</table>

Notes: *adapted from the Joint Societies UK Guidelines for identification, management and referral — Chronic kidney disease in adults⁶; **Stage 3 CKD should be subdivided following publication of NICE 73: Chronic kidney disease.⁶
April 2007 and April 2008 (available at www.renal.org/pages/pages/clinical-affairs/guidelines.php). Other national guidelines commonly used in UK renal units include the European Renal Association/European Dialysis and Transplant Association’s (ERA/EDTA) — European best practice guidelines (EBPG) and the US National Kidney Foundation’s (NKF) — Kidney disease outcomes quality initiative (KDOQI) clinical practice guidelines.4

Furthermore, Kidney Disease Improving Global Outcomes (KDIGO) was established in 2003 with the aim of promoting worldwide coordination, collaboration, and integration of initiatives to develop and implement clinical practices guidelines.5 The KDIGO website has a nephrology guideline database that enables easy access to existing global clinical practice guidelines from a single site; available at http://www.renal.org/pages/pages/clinical-affairs/nephrology-guideline-database.

CKD is usually accompanied by, or is the result of, a number of co-morbidities, namely hypertension, diabetes and cardiovascular disease (CVD). Therefore, many existing UK disease-specific guidelines including those issued by the National Institute for Clinical Excellence (NICE) and National Service Frameworks (NSFs) will also be applicable to a proportion of the CKD population. The most recent guidance for this patient group was published by NICE in September 2008, (CG 73: Chronic kidney disease)6 and focuses on early identification and management of CKD in adults in both primary and secondary care. In addition, NICE has published a number of specific guidelines for the management of CKD complications, including guidelines on Anaemia management in CKD (CG39)7 and the technology appraisal of cinacalcet in secondary hyperparathyroidism (TA117).8

Estimated glomerular filtration rate (eGFR) in the identification, classification and management of CKD

After the UK adopted the US KDOQI programme for the classification of CKD, the Department of Health now recommends routine reporting of eGFR by all NHS clinical biochemistry laboratories. This has done much to improve the recognition of early CKD in patients in whom the reporting of serum creatinine levels alone may have missed. Following international acceptance, the eGFR now forms the basis for the classification and management of CKD. You may therefore wonder whether this means that pharmacists can consign creatinine clearance (CrCl) and the Cockcroft and Gault equation to a dim and distant past.

The first article1 described the importance of calculating an ‘appropriate estimate of the patient’s glomerular filtration rate (GFR) when dosing drugs that rely on the kidney for elimination as either:

1. CrCl using the Cockcroft and Gault equation, or
2. correction of the laboratory reported normalised eGFR to the patient’s actual, non-normalised eGFR (GFRactual).

The article described the potential for error if eGFR values were used inappropriately (i.e. uncorrected to GFRactual) for drug dosing.1 Ironically, for most of the common pharmacological interventions in the management of CKD itself prescribed doses do not usually require the calculation of an ‘appropriate estimate’ of GFR because these drugs are titrated against either a physiological parameter or a measurable clinical response. For example, the dose of a phosphate-binder will be determined by the patient’s serum phosphate level and response to the initial dose. Similarly, antihypertensives are titrated against blood pressure response despite some of the drugs (like enalapril and perindopril) being reliant on the kidney for elimination. In these circumstances, the eGFR provides a useful guide to the likely complications for a particular stage of CKD and prompts appropriate screening, management or pharmacological intervention (Table 1).9

CKD is accompanied by a multitude of symptoms and co-morbidities and so an appreciation of the effect of the failing kidney on a prescribed drug’s pharmacological and toxicological effects will be needed. In these circumstances, reliance on the clinical response to direct accurate drug dosing would not be appropriate, so calculating an appropriate estimate of GFR is essential. For example, over-cautious dosing of a renally cleared antibiotic for life-threatening sepsis cannot subsequently be titrated up in response to therapeutic failure. Similarly, a CKD patient with a CrCL of around 35ml/min prescribed gabapentin for a diabetic neuropathy, will need a reduction in the maximum total daily dose from 2400mg/day to 600mg/day to avoid subsequent toxicity.10

Two important adaptations to the K/DOQI classification systems have been recommended in NICE guidance 73: Chronic kidney disease6 The first is that stage 3 CKD should be split into two subdivisions as follows:

- Stage 3A (GFR 45–59 ml/min/1.73m²)
- Stage 3B (GFR 30–44ml/min/1.73m²)

This differentiates those people in whom a GFR below 45ml/min/1.73m² is

above: Hypertension is more common in people with chronic kidney disease

Pharmaceutical care is an essential component to the multidisciplinary approach of managing renal disease and much opportunity exists for pharmacists to benefit the health and well-being of CKD patients.
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CKD is usually accompanied by, or is the result of, a number of co-morbidities, namely hypertension, diabetes and cardiovascular disease.

Associated with a considerably increased risk of mortality and cardiovascular events. However, people aged more than 70 years with a stable eGFR in the range 45–59 ml/min/1.73m² that do not have other evidence of kidney damage are unlikely to be associated with CKD-related complications.

The second recommendation is that suffix ‘p’ should be used when staging CKD to denote the presence of proteinuria (defined for the purposes of this classification as urinary albumin:creatinine ratio (ACR) of ≥30 mg/mmol or protein:creatinine ratio (PCR) of ≥50 mg/mmol) to emphasise the importance of this as a risk factor both for the progression of CKD and for CVD.

Common complications of CKD

CKD progression and CVD risk

Disease background: Early CKD, described as CKD stages 1 to 3, is estimated to affect 10% of the UK population (half will have reached CKD stage 3), increasing to approximately 20% over 65 years and more than 30% over 80 years. Although the vast majority of early CKD patients do not progress to ERF, the majority of dialysis-dependent patients will have progressed from earlier stages of CKD. However, both micro- and macro-albuminuria are stronger predictors of cardiovascular mortality than of end-stage renal failure. In fact, only a minority of patients with microalbuminuria will progress to end-stage renal failure, because death from a cardiovascular cause commonly occurs before renal failure has developed, emphasising the importance of a holistic approach to therapy when managing these patients.

NICE guidance for the early identification and management of CKD disease in adults in primary and secondary care clearly sets out referral criteria for patients needing specialist renal services.

Equally, the guidelines advocate the role of primary care in managing the risk factors for disease progression and for CVD in all early CKD patients who do not necessarily need referral. Early recognition of CKD should encourage changes to prescribing, directing greater attention to meticulous hypertension control and pharmacological intervention to slow or prevent disease progression and reduce CVD risk. The pharmacotherapy recommend in the NICE guidelines for managing these aspects of CKD are summarised in Table 2.

Therapeutic targets are given in Table 2.

Practice point to consider: These guidelines are generally consistent with other UK guidelines and are designed to be integrated into existing management systems for cardiovascular risk, hypertension and diabetes (e.g. NICE CG34 and GC66). Readers are encouraged to refer to the full guidelines for further details.

Medication reviews are essential in patients with CKD. Pharmacists should screen prescription records for:

- the absence of any therapies that may be beneficial to prevent disease progression

Table 2. Summary of recommended pharmacotherapy for CKD progression and CVD risk.6,9

<table>
<thead>
<tr>
<th>Control of hypertension:</th>
<th>Choice of antihypertensive agent (according to presence or absence of diabetes, CKD, proteinuria, hypertension and CVD):</th>
</tr>
</thead>
<tbody>
<tr>
<td>In CKD: keep systolic below 140mmHg (target range 120–139mmHg) and diastolic below 90mmHg</td>
<td>Anti-hypertensive</td>
</tr>
<tr>
<td>In CKD + Diabetes or</td>
<td>ACE Inhibitor/ARB</td>
</tr>
<tr>
<td>ACR ≥70 mg/mmol: keep</td>
<td>ACE Inhibitor/ARB</td>
</tr>
<tr>
<td>systolic below 130 mmHg</td>
<td>ACE Inhibitor/ARB</td>
</tr>
<tr>
<td>(target range 120–129mmHg) and diastolic below 80mmHg</td>
<td>Choice according to</td>
</tr>
</tbody>
</table>

- Stop ACE inhibitor/ARB if K+ ≥ 6 mmol/l and other drugs known to promote hyperkalaemia.

- Stop ACE inhibitor/ARB if K+ ≥ 5 mmol/L – investigate and treat causes of hyperkalaemia and re-check K+.

- One-to-two weeks after starting and after each dose increase.

- If drop in eGFR from baseline is ≥25% or plasma creatinine increases by ≥30%:
  - Investigate other causes of deterioration, such as volume depletion or concurrent medication (such as NSAIDs).
  - If no other cause for deterioration stop the ACE inhibitor/ARB or reduce dose to a previously tolerated lower dose, and add an alternative antihypertensive medication if needed.

- If hyperkalaemia present:
  - Stop ACE inhibitor/ARB if K+ ≥ 6 mmol/L and other drugs known to promote hyperkalaemia (such as NSAIDs or potassium-sparing diuretics) have been discontinued.

Cardiovascular prophylaxis:

- Statin therapy for primary prevention of CVD in people with CKD should not differ from its use in people without CKD and should be based on existing risk tables for people with and without diabetes (bearing in mind that the Framingham risk tables significantly underestimate risk in people with CKD).

- Offer statins for the secondary prevention of CVD irrespective of baseline lipids.

- Offer antiplatelet drugs for the secondary prevention of CVD.
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Derangements in bone mineral metabolism

Disease background: Derangements in bone mineral metabolism are common in CKD and can present early in CKD stage 3. The intricate relationship between phosphorous, calcium, parathyroid hormone (PTH) and vitamin D is under the delicate homeostatic control of the kidneys.

Typically, as CKD advances, patients have abnormal serum calcium levels, hyperphosphataemia, low calcitriol levels and rising levels of PTH (secondary hyperparathyroidism). Symptomatically, patients may experience bone and muscle pain, abnormalities of joints, fractures and itching of the skin and eyes. Further complications result from metastatic extraskeletal calcification of soft tissue, CVD, renal osteodystrophy, calciphylaxis and an increased mortality risk. If left untreated, hyperphosphataemia, reduced calcitriol, and hypocalcaemia result in parathyroid hyperplasia. As a consequence, the gland becomes less responsive to suppression with calcium and calcitriol, and refractory secondary hyperparathyroidism can result in the need for a parathyroidectomy.

Therapeutic targets: Four biochemical markers are used to assess the presence and progression of the disease: serum corrected calcium (CCa), phosphate (Phos), calcium x phosphate product (calculated by multiplying calcium and phosphate levels) and PTH. Typical reference ranges for the general population differ from the CKD target ranges, which are specific to the stage of CKD. Target ranges also differ depending on which national guidelines are used. Typical reference ranges for the UK are summarised in Table 3. Although the Renal Registry annually audits UK renal units against these targets, some units follow the US K/DOQI guidelines, which advocate tighter controls and provide integrated clinical action plans for its management. KDIGO are due to publish their guidelines in 2009.

Therapeutic options: Early management of disturbances in mineral and bone metabolism is essential for the long-term well-being and longevity of patients. However, current NICE guidance does not recommend routine measurement of calcium, phosphate, PTH and vitamin D levels in people with stage 1, 2, 3A or 3B CKD. The Renal Association recommends the monitoring of PTH begins at CKD stage 3 if the CKD is progressive. The pharmacological management is summarised in Table 4.

Phosphate binders

Patients are referred for dietetic advice to restrict dietary phosphate intake, but this must be balanced against adequate protein.
intake. As CKD progresses, phosphate-restricted diets are usually insufficient to control serum phosphate and most patients will require phosphate binders that act by binding to phosphate in the gut to prevent its absorption. The choice of binder therapy is generally based on relative efficacy, side-effect profile, cost and patient preference/compliance. Until the mid-1980s, aluminium was the main phosphate binder used until realisation of its toxic side-effects such as osteomalacia and dementia led to it being reserved for short periods in patients who are not controlled by other means. Calcium-based binders are reasonably effective and relatively cheap and in many units represent first-line therapies. Fears of excess calcium load, especially in the dialysis population, may lead to limitations in dose and often non-calcium based binders are supplemented to achieve phosphate control. Sevelamer is a non-metal, non-calcium polymer that may have additive advantages with its ability to bind cholesterol in the gut, although to what extent this benefit produces improvements in patient-oriented outcomes is yet to be established. Sevelamer is not a particularly strong binder and is only available currently as an 800mg tablet. Consequently the tablet burden is high (1–5 tablets per meal) which may have a negative impact on patient compliance and the cost is typically several thousand pounds per patient per year. Never-the-less this is a relatively safe, effective and widely used treatment option. Recently licensed is lanthanum carbonate, a rare earth metal. Safety concerns with aluminium have led to close scrutiny of the safety data of lanthanum. However, lanthanum does not rely on the kidney for its elimination and it is minimally absorbed from the gut. Lanthanum carbonate is available in a range of strengths and has the advantage of a lower tablet burden. It is also relatively costly when compared to calcium-based binders, but is a welcome addition to the therapeutic options for managing hyperphosphataemia. Despite the routine use of phosphate binders in CKD stages 3, 4 and 5, they are licensed for use only in dialysis-dependent patients.

**Vitamin D**

Vitamin D therapy may be started in CKD, either in response to low serum calcium or to elevations in PTH. Renal hydroxylation is likely to be normal in early CKD (stages 1, 2A and 3B) and therefore NICE guidance recommends ergocalciferol or cholecalciferol as the first treatment for vitamin D deficiency in this population. In advanced stages of CKD, vitamin D supplementation is provided with alfacalcidol (1-alpha-hydroxycholecalciferol) or calcitriol (1,25-dihydroxycholecalciferol) so that it does not require activation (hydroxylation) by the kidney. Vitamin D suppresses the secretion of PTH directly through receptors on the parathyroid gland and indirectly through elevations in calcium by increasing intestinal absorption. However, it is not always possible to titrate vitamin D supplements sufficiently to suppress PTH without elevating calcium above target levels. Equally, it is important not to over-suppress PTH below target level for a given stage of CKD because this runs the risk of inducing adynamic bone disease. Without sufficient levels of PTH, bone remodelling is reduced, and the buffering capacity of the bones to excess serum calcium and phosphate is lost, encouraging extra-skeletal deposition. Low turnover bone disease is

### Table 3. Typical reference ranges for the general population and the Renal Association’s bone mineral metabolism targets

<table>
<thead>
<tr>
<th>Complication</th>
<th>Reason (Reduced renal ultrafiltration of phosphorous)</th>
<th>Calculated diet (1 table per meal)</th>
<th>Pharmacological therapy</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperphosphataemia</td>
<td>Reduced 1-alpha-hydroxylase activity: 1. reduced functional renal tissue</td>
<td>Calcium supplementation</td>
<td>Active (1-alpha-hydroxylated) Vit. D Calcium supplementation</td>
<td>Calcium carbonate (Calcichew®) Calcium acetate (Phosex®) Sevelamer (Renagel®) Lanthanum carbonate (Fosrenol®) Aluminium hydroxide (Aluncap®) Alfacalcidol (One-Alpha®) Calcium carbonate (Calcichew®)</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>Reduced functional renal tissue</td>
<td></td>
<td>Active (hydroxylated) Vit. D</td>
<td>As above</td>
</tr>
<tr>
<td>Secondary hyperparathyroidism</td>
<td>Persistent hyperphosphataemia, Decreased calcitriol production</td>
<td>Vitamin D analogues</td>
<td>Active (hydroxylated) Vit. D</td>
<td>Alfacalcidol (One-Alpha®) Paricalcitol (Zemplar®) Cinacalcet (Mimpara®)</td>
</tr>
<tr>
<td>Refractory secondary hyperparathyroidism</td>
<td>Persistent hypocalcaemia, Glandular hyperplasia due to poor control of secondary hyperparathyroidism</td>
<td>Cacimimetic agent</td>
<td>Active (hydroxylated) Vit. D</td>
<td>As above</td>
</tr>
</tbody>
</table>
Therapeutic options

CKD is accompanied by a multitude of symptoms and co-morbidities and so an appreciation of the effect of the failing kidney on a prescribed drug’s pharmacological and toxicological effects will be needed.

becoming more frequent among the dialysis population and particular attention is needed to ensure patients are kept within the target PTH range for their stage of CKD.

Recent pharmaceutical additions
Two recent additions to the UK market have increased the therapeutic options for managing disturbance in bone mineral metabolism of CKD.

Paricalcitol (a structural analogue of vitamin D) is available for IV and oral administration and is indicated for the prevention and treatment of secondary hyperparathyroidism associated with CKD. Paricalcitol has been shown to reduce PTH levels and the manufacturers claim to have minimal calcaemic and phosphatemic effects on the intestines, (which can be a limitation to conventional vitamin D therapy, since unwanted elevations in calcium and phosphate can occur well before PTH is sufficiently suppressed). However, careful monitoring of serum calcium and phosphate is advocated in the Summary of Product Characteristics (SmPC) for paricalcitol.

Cinacalcet is a calcimimetic that directly suppresses PTH levels by increasing the sensitivity of the calcium sensing receptor on the parathyroid gland to extracellular calcium. Although licensed for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) receiving maintenance dialysis, its use is limited by the criteria set out in current NICE guidelines, which advocate reserving its use for patients with refractory secondary hyperparathyroidism only if PTH levels are greater than 85 pmol/L and if serum corrected calcium levels are normal or high, and in whom a parathyroidectomy is contraindicated.

Practice point to consider: Early management of derangements in bone mineral metabolism of CKD is essential for the long-term control and well-being of patients. Treatment adds significantly to the tablet burden for the CKD patient and when coupled with fluid restriction, may further affect patient compliance. Early in the course of the disease patients may not experience any symptoms and rarely associate symptoms like bone pain or itching with the disease state. Hence, many patients do not fully understand the reasons for taking these drugs. Reinforcing the benefits of therapy and continued education about the long-term complication of non-compliance is therefore an essential component of the pharmaceutical care offered by pharmacists to help ensure concordance. Patients should be counselled about the appropriate timing of taking binders in relation to food to maximise efficacy and reduce side-effects. Medicines usage review for these therapies can be of value not only for maximising patient management but for curtailing unnecessary health care expenditure if non-compliance issues are communicated to the prescriber.

Anaemia

Disease background: For most patients with progressive CKD anaemia is an inevitable complication and accounts for many of the symptoms and treatment costs. The main reason CKD patients develop anaemia is inadequate production of the hormone erythropoietin in the peritubuar fibroblasts of the kidney. Anaemia is also exacerbated by iron deficiency, infection, chronic inflammation and hyperparathyroidism. Because of its insidious onset patients may be asymptomatic at the point of diagnosis of anaemia. Treating renal anaemia improves physical capacity, cognitive function and general well-being and improves physiological functions including the cardiac and immune systems.7

The NICE guidelines on anaemia management7 in CKD is endorsed by the Renal Association. The Renal Association recommend that anaemia in adult patients with CKD should be evaluated when:

- Hb<13g/dl in adult males and post-menopausal females
- Hb<12g/dl for pre-menopausal females.

Also, CKD should be considered as:

- a possible cause when GFR is <60 ml/min/1.73m² (CKD stage 3)
- a likely cause when GFR is <30 ml/min/1.73m² (<45 in diabetics) when no other causes such as blood loss, folic acid or B12 deficiency can be identified.

Therapeutic targets (NICE guidelines7)

Erythropoietin-stimulating agents (ESA) should:

- be started if Hb falls to 11g/dl
- achieve a target Hb of 10.5–12.5 g/dl
- be adjusted when Hb >12.0 or <11.0 g/dl

Concurrent iron therapy should maintain serum ferritin between:

- 200–500mcg/l in haemodialysis patients
- 100–500mcg/l in non-haemodialysis patients

and either a:

- transferrin saturation (TSATs) >20% (unless ferritin is greater than 800mcg/l) or
- percentage hypochromic red cells (%HRC) of <6% (unless ferritin is greater than 800mcg/l).

More recently, in response to the findings of the CHOIR and CREATE studies, MHRA suggests a lower target Hb range of 10–12 g/dl and advises that Hb levels should not be increased beyond that which provides adequate symptom control, which in some patients will be below its recommended range.13

This places less emphasis on Hb target-
chasing and creates disparity between targets set by national clinical guidelines and the regulatory body. The MHRA also advise against raising Hb levels greater than 12g/dl, because over-correction of Hb concentration in CKD patients may increase the risk of death and serious cardiovascular events.

**Therapeutic options**
With the advent of recombinant DNA technology ESAs have enabled the correction of anaemia of CKD and has led to a significant reduction in transfusion requirements. Although haemoglobin levels provide the overarching measure of anaemia management, optimising ESA therapy with appropriate iron repletion is both clinically and cost-effective. Periodic iron studies should be interpreted along with regular monitoring of Hb levels.

**Iron therapy:** Oral iron therapy with periodic IV ‘top-up’ is usually adequate in pre-dialysis and peritoneal dialysis patients. For the haemodialysis population iron is invariably provided as IV therapy, either in the form of iron sucrose (Venoferr®) or iron dextran (Cosmofer®), which may be administered directly into dialysis circuits.

**Iron studies:** Measurement of serum ferritin ensures patients have adequate iron stores and are not suffering from an ‘absolute iron deficiency’. However, ferritin levels are sensitive to inflammatory processes and even values as high as 800mcg/l are rarely indicative of iron overload. Although patients may have adequate iron stores the stimulation of erythropoiesis with ESAs can result in the demand for iron outweighing the rate of mobilization — referred to as ‘functional iron deficiency’.

**Erythropoietin stimulating agents**
The erythropoietin pharmaceutical market is arguably the world’s most successful: by the end of 2005 it was in excess of US$ 12 billion and is expected to exceed US$ 20 billion by 2020. Despite the patent expiry of many brands this market remains very lucrative for the originator companies, mainly because large pockets of the global market remain relatively impenetrable to ‘generic’ alternatives. The premiums these drugs generate add significant financial burden to health care providers. Originator products have evolved from short-acting agents to longer-acting agents with improved stability.

*First generation:* The first generation of ESA are the recombinant erythropoietins, also known as epoetins. Epoetin-alfa (Eprex®) and epoetin-beta (NeoRecormon®) were the first in this generation of ESA and formed the mainstay therapy. The manufacturers’ recommended initial dosing schedule for these drugs are based on thrice weekly administration calculated on IU/kg bases, but in reality most patient are started on simpler regimens of 2000–3000IU administered two to three times per week, which represents the availability of pre-filled syringe strengths. One disadvantage of the short-acting epoetins is the relatively frequent administration, although in the maintenance phase of treatment epoetin-beta may be given once-weekly or even once fortnightly in stable patients. In pre-dialysis and peritoneal dialysis patients epoetins are administered via the subcutaneous (SC) route. For haemodialysis patients, epoetins can be administered painlessly by the IV route using the vascular access already established for dialysis. However, epoetins are 20–30% more efficient when given SC compared with IV and are therefore more cost-effective via the SC route than IV.² ² ² ² However, the SmPC for eprex states that ‘in patients with chronic renal failure where intravenous access is routinely available (haemodialysis patients) administration by the intravenous route is preferable.¹⁴ Epoetin-delta (Dynepo®) was a late addition to this generation of ESAs, but failure to make inroads into the market resulted in a European-wide withdrawal mid 2008.

*Second generation:* Darbepoetin-alfa (Aranesp®) is the first of the second generation ESAs. With its larger molecular weight and longer elimination half-life it requires less frequent dosing than the epoetins. The once-weekly initiation phase is followed by a once fortnightly or even once-monthly maintenance phase in the pre-dialysis population. The approximate conversion ratio is darbopoetin-alfa 1mcg to epoetin 200IU. There seems to be little if any difference between the efficacy of SC and IV administration routes for darbopoetin-alfa.⁷

Methoxy polyethylene glycol-epoetin beta (Mircera®) is a newly marketed continuous erythropoietin receptor activator. The larger molecular size and different receptor binding affinity allows once monthly administration in all CKD patients (once per fortnight for initiation). Another advantage of Mircera® is the ability to store it at room temperature for up to 31 days. Clinical experience with Mircera® is limited at present and its exact place in therapy is yet to be established, but early results are encouraging.

**Biosimilars:** The EU regulatory body, the EMEA, has led the way in the approval procedure for later versions of off-patent biopharmaceuticals, which they have termed ‘biosimilars’.¹⁵ ¹⁶ In the US, the FDA have adopted the term ‘follow-on biologics’ but at present no regulatory pathway exists for US approval of these agents. Biosimilar epoetins already available in the UK include Epoetin-zeta (Retacrit®) and Epoetin-alfa (Binocrit®). Although pre-marketing studies of biosimilars are likely
Therapeutic options

to ensure clinical efficacy comparable to that of the innovator product, they are unlike to identify potentially rare adverse events. It may be many years before the safety profile of biosimilars is established from pharmacovigilance and post-market surveillance. Pharmacists will be familiar with the concept of generic drugs, but in this relatively new era of biopharmaceuticals pharmacists are now faced with the prospect ensuring the quality, safety and efficacy of the ‘biosimilars’ they dispense. Unlike the simple chemical structures of traditional drug therapies, biopharmaceuticals comprise complex and inherently unstable protein structures that are difficult to characterise analytically and have efficacy, safety and immunogenicity heavily dependent on good (patented) reproducible manufacturing methods. Defining ‘similarity’ for these products has been a challenge for the regulatory authorities in the licensing of biosimilars.

**Practice point to consider:** Anaemia management of CKD is a complex and very expensive process. Most of the management in the UK is based in secondary care where designated anaemia co-ordinators (usually specialist nurses) are responsible for prescribing and monitoring therapy. Although the difference in the ESA described above is important in the choice of agent for individual patients, most regional renal units will have a contract price for a particular ESA, which most of their patients will receive. Hospital pharmacists usually play an integral role in the contractual side of funding and ‘procurement deals’, and in some units they are responsible for prescribing and clinical management. Although many units provide out-patient ESA therapy through home delivery services others may opt for GP prescribing under ‘shared-care’ arrangements. For community pharmacists who are presented with such prescriptions it is essential to develop a good rapport with both the prescriber and the patient if continuity of supply and communication of regular dose alteration are to succeed. Patients should be counselled on the need to maintain the cold chain and what to do in the event that it is broken, how to dispose of used syringes, and to communicate changes in doses to all those involved in the management and supply of their therapy to avoid unnecessary wastage. With the availability of biosimilars pharmacists should be mindful not to inadvertently substitute products, because these products are not interchangeable. Clarification of the prescriber’s intention is necessary for any ambiguous prescriptions. To ensure traceability and to prevent inappropriate substitution EU law requires every biosimilar to either have a proprietary brand name or the name of the active substance together with the company name, for example, ‘Epoetin alfa Hexal (Epoetin alfa) from Hexal Biotech’.

**Conclusion**

Routine reporting of eGFR by NHS clinical biochemistry laboratories has done much to improve the recognition of early CKD in patients and now forms the basis for identification, classification and management of CKD. With an appreciation of the likely complications for a given stage of CKD the eGFR prompts for appropriate screening and management. However, it is not without its pitfalls and the most obvious from a pharmaceutical point of view is the confusion surrounding its appropriate use for drug dosing. Pharmacological intervention plays a key role in all stages of CKD, many of which will have anomalous dosage regimens, and so pharmacists are uniquely placed to contribute a pivotal role in multidisciplinary approach to patient management.

**Declarations of interest**

The author wishes to state that he has sat on advisory boards for Ortho-Biotech and Roche and has spoken at Roche sympoisa.

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