Anaemia management in chronic kidney disease patients: an overview of current clinical practice

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Abstract

This paper describes three recent, related surveys of anaemia management practice in patients with chronic kidney disease, with particular emphasis on initiation of epoetin therapy. It also compares current practice with the European Best Practice Guidelines (EBPG) for anaemia management. The European Survey of Anaemia Management (ESAM) was a 6 month, longitudinal prospective survey of anaemia management in dialysis patients. Although most survey data concerned patients already on dialysis, some retrospective data concerned initiation of dialysis and epoetin therapy. These findings led to the Predialysis Survey of Anaemia Management (PRESAM), a cross-sectional, retrospective survey of patients beginning dialysis, focusing on referral to renal centres and anaemia management in the year preceding dialysis. The Early Renal Insufficiency Referral Survey (ERIRS) is a further cross-sectional survey currently in progress, investigating referral practices during pre-dialysis care. Collectively, these three surveys provide a wealth of data about pre-dialysis anaemia management. ESAM included data from 14,527 patients, PRESAM from 4,333 patients, and data from 724 patients enrolled in ERIRS have been analysed. The evidence indicates that, at the time of referral to a renal centre, most patients have haemoglobin concentrations well below the levels recommended by the EBPG. Haemoglobin concentrations are lowest in patients referred within the month prior to the initiation of dialysis. Most patients do not start epoetin treatment until dialysis is initiated, despite having haemoglobin concentrations below the level recommended by the EBPG for the initiation of epoetin. Patients who are referred earlier (i.e. those under the care of the renal centre nephrologist for more than a month before the initiation of dialysis) tend to have higher haemoglobin concentrations and are more likely to be receiving epoetin therapy. Such patients are in the minority, however, indicating that pre-dialysis anaemia management practices continue to fall short of the recommendations of the EBPG.

Keywords: anaemia; chronic kidney disease; dialysis; epoetin; haemoglobin; patient referral

Introduction

The ability to treat anaemia with recombinant human erythropoetin (r-HuEPO, epoetin) represents a considerable step forward in the management of patients with chronic kidney disease. Epoetin, initiated either before or after the start of dialysis, improves patients’ functional state and quality of life, and may also reduce morbidity and mortality.

In 1996, the US National Kidney Foundation published the evidence-based Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [1], describing how to diagnose and treat anaemia in patients both before and after the initiation of dialysis. More recently, in 1998, the European Dialysis and Transplant Association (EDTA) published the European Best Practice Guidelines (EBPG) for the treatment of anaemia [2]. Like the DOQI guidelines, the EBPG were based on the three levels of evidence specified by the US Agency for Health Care Policy and Research. By reviewing an additional 200 publications, the EBPG updated the K/DOQI recommendations, and approached the diagnosis and treatment of anaemia from a European point of view.

The European Survey on Anaemia Management (ESAM) [3], published in 2000, compiled prospective epidemiological data on the treatment of anaemia in a selected group of patients receiving haemodialysis or peritoneal dialysis in 14 European countries ($n = 14,527$). ESAM revealed that only a small proportion of patients began treatment with epoetin before dialysis (i.e. only 11% received epoetin before they started on haemodialysis). ESAM also revealed that patients had low levels of haemoglobin at the start
of epoetin treatment (<9 g/dl), and that low target levels were achieved after treatment.

Two further surveys have been designed subsequently with a specific focus on patients with chronic kidney disease: the Predialysis Survey on Anaemia Management (PRESAM) and the Early Renal Insufficiency Referral Survey (ERIRS). PRESAM was designed to assess the care given to patients prior to the start of haemodialysis or peritoneal dialysis. The survey fulfilled two objectives: first, to observe the European pattern of referral of patients with chronic kidney disease to nephrologists prior to the start of dialysis; and secondly, to investigate the diagnosis and treatment of anaemia in these patients. The ERIRS is a cross-sectional survey currently in progress, which also investigates referral practices during pre-dialysis care.

Survey methodology and analysis

ESAM was a prospective, observational survey that included 14,527 patients on haemodialysis or peritoneal dialysis who were receiving epoetin [3]. This represents nearly 10% of the participating countries’ dialysis population. Participating centres from 14 countries were asked to include randomly 30% of all ‘Monday dialysis’ patients (20% in France and Germany), and these patients were followed monthly for 6 months between September 1998 and March 1999. Both PRESAM and ERIRS were designed as retrospective, observational studies. PRESAM included 4333 patients who started haemodialysis or peritoneal dialysis between 1 September 1999 and 30 November 1999. The participating 779 centres from 23 countries were asked to include all patients who met these inclusion criteria. Data were retrieved covering the year before the start of dialysis. Data collected concerned referral and dialysis initiation, co-morbidities, major clinical events and drug treatment, including epoetin treatment.

Centres from 16 countries participating in ERIRS (which is still in progress) were asked to exclude patients starting dialysis and emergency patients, but to include renal patients seen for the first time in a nephrology out-patient clinic between 27 November 2000 and 1 December 2001. The survey period was from <2 months before referral to the first visit. Data collected concerned referral, including reasons for referral and demographic and clinical data from patients at the time of referral, as well as kidney function and anaemia.

Demographics

Of the 14,527 patients in ESAM, 54.3% were men and the overall mean age was 61.1 ± 15.3 years. In PRESAM, 58.9% of the 4333 patients were men, and the overall mean age at first visit to the nephrologist was 55.7 ± 17.2 years. Of the 724 patients in ERIRS for whom data have been analysed so far, 55.4% are men and the overall mean age is 58.2 ± 16.1 years. In established dialysis patients (ESAM), the most common aetiology of renal failure was chronic glomerulonephritis (25.5%), followed by diabetic nephropathy (17.7%), renovascular disease (13.9%) and tubulo-interstitial disease (13.3%) [3]. Less common causes included polycystic kidney disease, hereditary renal disease, failed renal transplant and multiple myeloma. For 17.3% of the patients, the cause of renal failure was undefined. Among new dialysis patients (PRESAM) and new patients attending an out-patient nephrology clinic (ERIRS), however, diabetic nephropathy was the most common cause, accounting for ~23% of patients in PRESAM and 20% in ERIRS. Chronic glomerulonephritis accounted for ~18 and 14%, respectively, of patients in these two surveys.

Referral pattern

Most of the patients in both PRESAM and ERIRS were referred by their family physician, by an internist or by other nephrologists (~25–30% in each category). Other referring physicians (a diabetologist or endocrinologist, geriatrician, cardiologist or a haematology specialist) accounted for very small numbers of patient referrals. Of note was the finding that diabetologists or endocrinologists were only responsible for ~5% of referrals in either survey. The majority of patients in PRESAM (57%) had been under the care of a nephrologist for >12 months prior to referral for dialysis. Nevertheless, a total of 43% of patients were under the care of a nephrologist for <12 months: 11% between 6 months and 1 year, 17% between 1 and 6 months and 15% for <1 month before they needed dialysis, indicating that a substantial proportion of patients are late referrals.

Renal function at the time of referral was generally poor. Creatinine clearance was >60 ml/min in only 20% of patients seen for the first time in an out-patient nephrology clinic (ERIRS). The majority of the patients had clinically important degrees of renal insufficiency at the time of referral. By the time of their first visit to a dialysis centre, the mean creatinine clearance of patients referred by another nephrologist was only 13.6 ± 11.4 ml/min, and that of patients referred by a non-nephrologist was 19.9 ± 18.1 ml/min (PRESAM).

Reflecting the poor renal function, haemoglobin levels at the time of referral were also poor. A majority of patients who started dialysis in PRESAM had a haemoglobin concentration <12 g/dl at the time of first visit to the dialysis centre, and only ~20% had a haemoglobin concentration ≥12 g/dl (Figure 1).
Furthermore, nearly 67% had a haemoglobin concentration <11 g/dl. In ERIRS, nearly 50% of patients had a haemoglobin concentration <12 g/dl at the time of first visit to the nephrologist, and nearly 26% had a haemoglobin concentration <11 g/dl. Overall in the two surveys, the haemoglobin concentrations at first referral confirm that many patients are late referrals for an adequate treatment of anaemia.

In patients who did not receive epoetin before dialysis (PRESAM and ERIRS) and who did not receive a transfusion in the month prior to dialysis, haemoglobin concentration on first visit to a dialysis centre was closely related to creatinine clearance. The relationship between haemoglobin concentration and serum creatinine, however, was much more variable. The relationship between haemoglobin concentration and creatinine clearance was similar in diabetic and non-diabetic patients. In both PRESAM and ERIRS, however, there were patients with a creatinine clearance of 80 ml/min who were anaemic and, conversely, with a creatinine clearance of 20 ml/min who were not anaemic.

**Co-morbidities and clinical events**

At the time of the first visit to a dialysis centre, many renal patients have important co-morbidities. For example, in PRESAM and ERIRS, almost 80% of patients had hypertension, >20% had coronary disease (and ~15% overt cardiac failure) and ~30% had diabetes mellitus. In PRESAM, it was noted that cardiac co-morbidity was related to age. Coronary disease almost doubled in prevalence between 51–64 and 75–84 years of age, while the prevalences of cardiac failure and arrhythmia both rose sharply with increasing age. The prevalence of hypertension, however, remained fairly constant.

When clinical events in the previous year were analysed in relation to the length of time under the care of a nephrologist (PRESAM), it was found that fewer patients who had been under a nephrologist for >1 year before dialysis experienced clinical events (cardiac events, ischaemic heart disease, transfusions, infectious disease) than those who were referred late (under the care of a nephrologist ≤1 month).

**Initiation of dialysis and epoetin treatment**

The percentage of patients starting haemodialysis was slightly higher in patients under the care of a nephrologist for <1 year, in agreement with previous reports [4,5], and was much higher than those starting peritoneal dialysis (only ~10%). Nearly 60% of all patients in PRESAM initiated haemodialysis with a native fistula for vascular access, and ~40% with a catheter. However, the percentage using a catheter was significantly higher in late-referred patients (under a nephrologist’s care ≤1 month) than in those under a nephrologist’s care for >1 year (~80% compared with ~30%).

At the start of dialysis, >90% of the patients in PRESAM had a haemoglobin level <11 g/dl, with a majority having concentrations <10 g/dl (Figure 2). The mean haemoglobin concentration was significantly higher in patients who had been under the care of a nephrologist for >1 year prior to starting dialysis than in those who had been under a nephrologist for
shorter periods of time, but nevertheless, the mean value was <10 g/dl.

Although a proportion of patients [11% (haemodialysis patients) and 31% (peritoneal dialysis patients) in ESAM [3] and 27% overall in PRESAM] started epoetin treatment before dialysis, the majority of patients started epoetin treatment either at the same time as dialysis (~30% in each survey) or after initiation of dialysis (>50% in ESAM, ~13% in PRESAM). At the time that epoetin treatment was initiated, haemoglobin concentrations were below those recommended (11 g/dl) by the EBPG in >95% of patients in both ESAM [3] and PRESAM, and were <10 g/dl in >80% of patients (Figure 3). At the first visit to the dialysis centre, the mean haemoglobin concentration was similar (~10 g/dl) in patients receiving or not receiving epoetin treatment (ESAM). The mean haemoglobin concentration of patients receiving epoetin at the start of dialysis remained ~10 g/dl, but importantly the mean haemoglobin concentration of patients not receiving epoetin had fallen to ~9 g/dl (PRESAM).

When ESAM was conducted, the stated target haemoglobin concentration in all the participating countries (11.2–12.3 g/dl) was broadly in line with the EBPG recommendations. When attainment of these targets at the start of dialysis was examined in PRESAM, however, no more than 20% of patients had reached a haemoglobin concentration >11 g/dl, irrespective of the length of time they were under the care of a nephrologist. About 70% reached the recommended serum ferritin concentration of 100 μg/l or more. Overall in ESAM (at the end of the study for patients with 6 months of follow-up) and PRESAM (at the start of dialysis), ~50% of patients had a haemoglobin concentration <11 g/dl.

Discussion and conclusions

PRESAM offered the opportunity to study a sample of 4333 incident patients in various European countries. This sample is epidemiologically valuable, in that all the patients starting dialysis in each centre were included. The mean age was 55.7 years, slightly lower than in ESAM (61.1 years). The difference may be explained by the fact that ESAM included prevalent patients, whereas PRESAM included only incident patients.

In ESAM, diabetic nephropathy was the second most common cause of renal insufficiency (17.7%), after chronic glomerulonephritis (25.5%). In contrast, the incident data from PRESAM showed diabetic nephropathy to be the most frequent cause of chronic kidney disease (23%), followed by chronic glomerulonephritis (18%). Diabetic nephropathy was also the most common cause of chronic kidney disease in ERIRS. PRESAM and ERIRS also found that significant co-morbidity was present commonly when patients were seen by a nephrologist in a dialysis centre for the first time. Hypertension was seen in ~80% of patients, coronary heart disease in 23% and heart failure in 15%. As might be expected, diabetic patients were more likely to suffer from co-morbidities than non-diabetic patients.

Encouragingly, in PRESAM, 57% of patients who started dialysis had been under the care of a nephrologist for more than a year. Only 14% had been referred in the month before starting dialysis. Thus, only a minority of patients in PRESAM could be considered as ‘late referrals’ [4,5]. Less encouraging, however, is the finding that most patients in PRESAM already had an extremely advanced degree of renal insufficiency at referral: the mean

Fig. 2. Haemoglobin concentration at the start of dialysis in patients enrolled in PRESAM.
creatinine clearance of patients referred by another nephrologist was only 13.6 ± 11.4 ml/min, and that of patients referred by a non-nephrologist was 19.9 ± 18.1 ml/min. Most patients (87%) started on haemodialysis; the remaining 13% started on peritoneal dialysis.

Notably, when patients saw the nephrologist for the first time, 69% already had haemoglobin concentrations <11 g/dl. Thus, even at this early stage, treatment with epoetin was already indicated according to the EBPG. The situation was even worse by the time patients finally started treatment with epoetin, when >90% of patients had haemoglobin concentrations <11 g/dl. By the time patients finally started treatment with epoetin, the mean haemoglobin was <9 g/dl. The haemoglobin values observed in PRESAM were very similar to those observed in ESAM, despite the fact that the ESAM patients started treatment some years earlier.

Patients under the care of a nephrologist for more than a year had significantly higher haemoglobin concentrations than those referred later. Even so, these patients started haemodialysis with an average haemoglobin <10 g/dl, well below recommended levels. Thus, inadequate treatment of the anaemia cannot be attributed solely to late referral, but must reflect a failure by some nephrologists to follow current guidelines.

In both PRESAM and ERIRS, in patients not treated with epoetin (who had not received transfusions in recent months), there was a correlation between haemoglobin levels and creatinine clearance. The greater the degree of renal insufficiency, the greater the degree of anaemia. However, there was wide variation between individuals, with a number of patients with a creatinine clearance of 80 ml/min who were anaemic, indicating that patients with relatively good renal function can be anaemic.

Contrary to the widespread belief that diabetic patients are more prone to develop severe anaemia as renal function declines, the relationship between haemoglobin and creatinine clearance was similar in diabetics and non-diabetics.

In PRESAM, 27% of patients received treatment with epoetin before starting dialysis. Similarly, Obrador et al. [6], in a review of >150,000 patients in dialysis in the USA, found that only 23% of patients received treatment with epoetin before starting dialysis. Notably, patients already on epoetin at the start of dialysis had higher haemoglobin concentrations than those not receiving epoetin (~10 g/dl vs 9 g/dl), though these levels are still much lower than those recommended by the EBPG. The average haemoglobin at the start of epoetin treatment was <9 g/dl in patients who started treatment after the initiation of dialysis.

The EBPG recommend an individual target haemoglobin >11 g/dl, with the aim of 85% of patients in the unit being above that level. In PRESAM, no more than 20% of patients had reached a haemoglobin concentration of >11 g/dl, irrespective of the length of time they were under the care of a nephrologist, indicating that the recommendations are not implemented.

In conclusion, PRESAM shows that many patients have extremely advanced renal insufficiency at referral, which may well invalidate attempts to delay the progression of chronic kidney disease and prevent co-morbidities. In fact, co-morbidities are extremely common, particularly in diabetic patients. PRESAM also reveals diabetes to be the most frequent cause of chronic kidney disease in patients today. Although being under the care of a nephrologist for over a year reduces the likelihood of cardiac complications, only a few patients receive treatment with epoetin.
prior to dialysis. Many patients start dialysis with severe anaemia. Treatment with epoetin often is initiated at haemoglobin concentrations far below those recommended by the EBPG, when patients have severe symptoms of anaemia. Haemoglobin targets recommended by the guidelines often are not achieved.

The value of surveys such as PRESAM and ERIRS lies in pointing the way to correct diagnosis and treatment of anaemia in chronic kidney disease. It is essential to recognize the many deleterious effects of renal anaemia, especially its role in the development of left ventricular hypertrophy and associated morbidity and mortality. Nor should we forget its deleterious effects on quality of life. The data presented here suggest that the risks of allowing renal anaemia to remain untreated are still not fully recognized. It is to be hoped that surveys such as PRESAM and ERIRS will draw attention to the risks of late treatment of anaemia, and help to improve anaemia management during the initial stages of chronic kidney disease. The ultimate objectives of treating anaemia are to improve quality of life, improve the patient’s prognosis and perhaps even to delay the progression of chronic kidney disease.

References